

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/001445

International filing date: 14 February 2005 (14.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 04004332.5
Filing date: 26 February 2004 (26.02.2004)

Date of receipt at the International Bureau: 24 March 2005 (24.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



Europäisches
Patentamt

European
Patent Office

EP05/D1445
Office européen
des brevets

Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

04004332.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Europäisches
PatentamtEuropean
Patent OfficeOffice européen
des brevets

Anmeldung Nr:
Application no.: 04004332.5
Demande no:

Anmeldetag:
Date of filing: 26.02.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

MERCK PATENT GmbH
Frankfurter Strasse 250
64293 Darmstadt
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Benzimidazolyl derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D235/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

l03224 do.doc

**Merck Patent Gesellschaft
mit beschränkter Haftung
6 4 2 7 1 D a r m s t a d t**

Benzimidazolyl derivatives

103224 do.doc

1

Benzimidazolyl derivatives

The present invention relates to benzimidazolyl derivatives, benzimidazolyl derivatives as medicaments, benzimidazolyl derivatives as inhibitors of raf-kinase, the use of benzimidazolyl derivatives for the manufacture of a pharmaceutical, a method for producing a pharmaceutical composition containing said benzimidazolyl derivatives, the pharmaceutical composition obtainable by said method and a method of treatment, comprising administering said pharmaceutical composition.

10

Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the p21^{ras}/raf pathway.

15

The p21^{ras} gene was discovered as an oncogene of the Harvey (rasH) and Kirsten (rasK) rat sarcoma viruses. In humans, characteristic mutations in the cellular ras gene (c-ras) have been associated with many different types of cancers. These mutant alleles, which render Ras constitutively active, have been shown to transform cells, such as the murine cell line NIH 3T3, in culture.

20

25

The p21^{ras} oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30 % of all human cancers (Bolton et al. (1994) Ann. Rep. Med. Chem., 29, 165-74; Bos. (1989) Cancer Res., 49, 4682-9). Oncogenic Ras mutations have been identified for example in lung cancer, colorectal cancer, pancreas, thyroid cancer, melanoma, bladder tumours, liver tumour, kidney tumor, dermatological tumours and haematological tumors (Ddjei et al. (2001), J. Natl. Cancer Inst.

30

93(14), 1062-74; Midgley, R.S. and Kerr, D.J. (2002) *Critical Rev. Onc/*
hematol 44, 109-120; Downward, J. (2003), *Nature reviews* 3, 11-22). In its
normal, unmutated form, the ras protein is a key element of the signal
transduction cascade directed by growth factor receptors in almost all tissues
5 (Avruch et al. (1994) *Trends Biochem. Sci.*, 19, 279-83).

Biochemically, ras is a guanine nucleotide binding protein, and cycling
between a GTP-bound activated and a GDP-bound resting form is strictly
controlled by ras endogenous GTPase activity and other regulatory proteins.
10 The ras gene product binds to guanine triphosphate (GTP) and guanine
diphosphate (GDP) and hydrolyzes GTP to GDP. It is the GTP-bound state of
Ras that is active. In the ras mutants in cancer cells, the endogenous
GTPase activity is alleviated and, therefore, the protein delivers constitutive
growth signals to downstream effectors such as the enzyme raf kinase. This
15 leads to the cancerous growth of the cells which carry these mutants
(Magnuson et al. (1994) *Semin. Cancer Biol.*, 5, 247-53). The ras proto-
oncogene requires a functionally intact c-raf1 proto-oncogene in order to
transduce growth and differentiation signals initiated by receptor and non-
receptor tyrosine kinases in higher eukaryotes.

20 Activated Ras is necessary for the activation of the c-raf-1 proto-oncogene,
but the biochemical steps through which Ras activates the Raf-1 protein
(Ser/Thr) kinase are now well characterized. It has been shown that
inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway
25 by administration of deactivating antibodies to raf kinase or by co-expression
of dominant negative raf kinase or dominant negative MEK also called ERK,
the substrate of raf kinase, leads to the reversion of transformed cells to the
normal growth phenotype see: Daum et al. (1994) *Trends Biochem. Sci.*, 19,
474-80; Fridman et al. (1994) *J Biol. Chem.*, 269, 30105-8. Kolch et al.
30 (1991) *Nature*, 349, 426-28) and for review Weinstein-Oppenheim et al.
Pharm. & Therap. (2000), 88, 229-279.

103224 do.doc

3

Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., Nat. Med. 1996, 2, 668-75; Geiger et al. (1997), Clin. Cancer Res. 3(7): 1179-85; Lau et al. (2002), Antisense Nucl. Acid. Drug Dev. 12(1): 11-20 ; McPhillips et al. (2001), Br. J. Cancer 85(11): 1753-8).

Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al. (1988) in The oncogene handbook; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184; Rapp, U.R., et al. (1990) Inv Curr. Top. Microbiol. Amunol. Potter and Melchers (eds), Berlin, Springer-Verlag 166:129-139).

Three isozymes have been characterized:

c-Raf (also named Raf-1, c-raf-1 or c-raf1) (Bonner, T.I., et al. (1986) Nucleic Acids Res. 14:1009-1015), A-Raf (Beck, T.W., et al. (1987) Nucleic Acids Res. 15:595-609), and B-Raf (Qkawa, S., et al. (1998) Mol. Cell. Biol. 8:2651-2654; Sithanandam, G. et a. (1990) Oncogene:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) Oncogene 5:345-351).

Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) Mol. Cell. Biol. 10:2503-2512; Rapp, U.R., et al. (1987) in Oncogenes and cancer S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific

103224 do.doc

4

Press, Tokyo). Microinjection into NIH 3T3 cells of oncogenically activated but not wild-type versions of the Raf-protein prepared with Escherichia coli expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in *Oncogenes and cancer*; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo; Smith, M. R., et al (1990) *Mol. Cell. Biol.* 10:3828-3833). Activating mutants of B-Raf have been identified in a wide range of human cancers e.g. colon, ovarian, melanomas and sarcomas (Davies, H., et al. (2002), *Nature* 417 949-945. Published online June 9, 2002, 10.1038/nature00766). The preponderant mutation is a single phosphomimetic substitution in the kinase activation domain (V599E), leading to constitutive kinase activity and transformation of NIH3T3 cells.

Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase in a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from a block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in *The Oncogene Handbook*, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) *Nature* (London) 320:540-543).

c-Raf function is required for transformation by a variety of membrane-bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) *Nature* (London) 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation (Morrison, D.K., et al. (1989) *Cell* 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) *Exp. Brain Res.* 84:403; Rapp, U.R., et al. (1988) *Cold Spring Harbor Sym. Quant. Biol.* 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:8855-8859), colony-stimulating factor (Baccarini, M., et al. (1990) *EMBO J.* 9:3649-3657). insulin

103224 do.doc

5

(Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12115-12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227), and interleukin 3 and granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

Upon mitogen treatment of cells, the transiently activated Raf-1 protein serine kinase translocates to the perinuclear area and the nucleus (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184). Cells containing activated Raf are altered in their pattern of gene expression (Heidecker, G., et al. (1989) in Genes and signal transduction in multistage carcinogenesis, N. Colburn (ed.), Marcel Dekker, Inc., New York, pp. 339-374), and Raf oncogenes activate transcription from Ap-1/PEA3-dependent promoters in transient transfection assays (Jamal, S., et al (1990) Science 344:463-466; Kaibuchi, K., et al (1989) J. Biol. Chem. 264:20855-20858; Wasylyk, C., et al. (1989) Mol. Cell. Biol. 9:2247-2250).

There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (KC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12131-12134; Kovacina, K.S., et al (1990) J. Biol. Chem. 265:12115-12118; Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859; Siegel, J.N., et al (1990) J. Biol. Chem. 265:18472-18480; Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by autophosphorylation or may be caused entirely by autophosphorylation initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) Science 233:305-312).

103224 do.doc

6

The process of angiogenesis is the development of new blood vessels, generally capillaries, from pre-existing vasculature. Angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased vascular permeability; (iii) subsequent dissolution of the basement membrane and extravasation of plasma components leading to formation of a provisional fibrin gel extracellular matrix; (iv) proliferation and mobilization of endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels.

10

Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood.

15

Normal angiogenesis is also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate or pathological angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; rheumatoid arthritis, and cancer. The role of angiogenesis in disease states is discussed, for instance, in Fan et al, Trends in Pharmacol Sci. 16:54-66; Shawver et al, DOT Vol. 2, No. 2 February 1997; Folkman, 1995, Nature Medicine 1:27-31.

20

In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkman, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.) Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great, unmet medical need.

25

Raf is involved in angiogenic processes. Endothelial growth factors (e.g. vascular endothelial growth factor VEGF or basic fibroblast growth factor bFGF) activates receptor tyrosine kinases (e.g. VEGFR-2) and signal through

30

103224 do.doc

7

the Ras/Raf/Mek/Erk kinase cascade and protects endothelial cells from apoptosis (Alavi et al. (2003), Science 301, 94-96; Hood, J.D. et al. (2002), Science 296, 2404; Mikula, M. et al. (2001), EMBO J. 20, 1952; Hauser, M. et al. (2001), EMBO J. 20, 1940; Wojnowski et al. (1997), Nature Genet. 16, 293). Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is upregulated in both tumor and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR- 2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., The Oncologist, Vol. 5, No. 90001, 3-10, April 2000).

Mice with a targeted disruption in the Braf gene die of vascular defects during development (Wojnowski, L. et al. 1997, Nature genetics 16, page 293- 296). These mice show defects in the formation of the vascular system and in angiogenesis e.g. enlarged blood vessels and increased apoptotic death of differentiated endothelial cells.

For the identification of a signal transduction pathway and the detection of cross talks with other signaling pathways suitable models or model systems have been generated by various scientists, for example cell culture models (e.g. Khwaja et al., EMBO, 1997, 16, 2783-93) and transgenic animal models (e.g. White et al., Oncogene, 2001, 20, 7064-7072). For the examination of particular steps in the signal transduction cascade, interfering compounds can be used for signal modulation (e.g. Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention may also be useful as reagents for the examination of kinase dependent signal transduction

103224 do.doc

8

pathways in animal and/or cell culture models or any of the clinical disorders listed throughout this application.

5 The measurement of kinase activity is a well known technique feasible for each person skilled in the art. Generic test systems for kinase activity detection with substrates, for example histone (e.g. Alessi et al., FEBS Lett. 1996, 399, 3, page 333-8) or myelin basic protein are well described in the literature (e.g. Campos-González, R. and Glenney, Jr., J.R. 1992 J. Biol. Chem. 267, Page 14535).

10

For the identification of kinase inhibitors various assay systems are available (see for example Walters et al., Nature Drug Discovery 2003, 2; page 259-266). For example, in scintillation proximity assays (e.g. Sorg et al., J. of Biomolecular Screening, 2002, 7, 11-19) or flashplate assays the radioactive phosphorylation of a protein or peptide as substrate with γ ATP can be measured. In the presence of an inhibitory compound no signal or a decreased radioactive signal is detectable. Furthermore homogeneous time-resolved fluorescence resonance energy transfer (HTR-FRET), and fluorescence polarization (FP) technologies are useful for assay methods. (for example Sillis et al., J. of Biomolecular Screening, 2002, 191-214).

15

20

Other non-radioactive ELISA based assay methods use specific phospho-antibodies (AB). The phospho-AB binds only the phosphorylated substrate. This binding is detectable with a secondary peroxidase conjugated antibody, measured for example by chemiluminescence (for exaple Ross et al., Biochem. J., 2002, 366, 977-981).

25

30

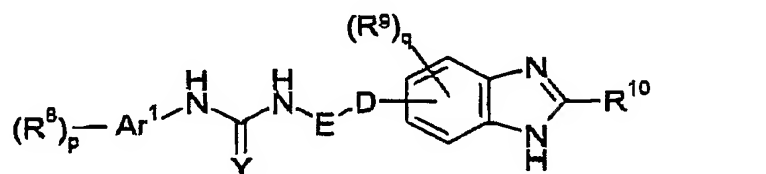
The present invention provides compounds generally described as benzimidazolyl derivatives, including both aryl and/or heteroaryl derivatives which are preferably kinase inhibitors and more preferably inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of p21^{ras}, the inhibitors preferably are useful in pharmaceutical compositions for human or

103224 do.doc

9

veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds preferably are useful in the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compound of Formula I or a pharmaceutically acceptable salt thereof can be administered for the treatment of diseases mediated by the raf kinase pathway especially cancers, preferably solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds preferably are useful in the treatment of complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus type1) induced immunodeficiency (Popik et al. (1998) J Virol, 72: 6406-6413) and infection disease, Influenza A virus (Pleschka, S. et al. (2001), Nat. Cell. Biol, 3(3):301-5) and Helicobacter pylori infection (Wessler, S. et al. (2002), FASEB J., 16(3): 417-9).

Therefore, subject of the present invention are benzimidazolyl derivatives of formula I



wherein

Ar^1 is selected from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic

10

heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

- 5 E is $(CR^5R^6)_n$, wherein n is 1 or 2,
- D is $(CR^5R^6)_k$, wherein k is 0 or 1,
- 10 R^5, R^6 are in each case independently from one another selected from H and A;
- R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, OHet, $N(R^{11})Het$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{13}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $CH=N-OA$, $CH_2CH=N-OA$, $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$.
- 15
- 20
- 25
- 30

I03224 do.doc

11

$\text{CH}=\text{CHCH}_2\text{NR}^{11}\text{R}^{12}$, $\text{CH}=\text{CHCH}_2\text{NR}^{11}\text{R}^{12}$,
 $\text{CH}=\text{CHCH}_2\text{OR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{CONH}_2$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{CONH}_2$, $(\text{CH}_2)_n\text{CHR}^{13}\text{COR}^{14}$,
 $(\text{CH}_2)_n\text{CHR}^{13}\text{COOR}^{14}$, $(\text{CH}_2)_n\text{CHR}^{13}\text{CH}_2\text{OR}^{14}$, $(\text{CH}_2)_n\text{OCN}$
 and $(\text{CH}_2)_n\text{NCO}$, wherein

- 5
 10 R^{11} , R^{12} are independently selected from a group consisting of H, A, $(\text{CH}_2)_m\text{Ar}^3$ and $(\text{CH}_2)_m\text{Het}$, or in $\text{NR}^{11}\text{R}^{12}$,
 R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S,
 15 R^{13} , R^{14} are independently selected from a group consisting of H, Hal, A, $(\text{CH}_2)_m\text{Ar}^4$ and $(\text{CH}_2)_m\text{Het}$,
 20 A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, preferably from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy and alkoxyalkyl.
 25 Ar^3 , Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal,
 30 NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{R}^{15}\text{R}^{16}$, $\text{S}(\text{O})_u\text{A}$ and OOCR^{15} .

I03224 do.doc

12

- 5 Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,
- 10 R¹⁵, R¹⁶ are independently selected from a group consisting of H, A, and (CH₂)_mAr⁶, wherein
- 15 Ar⁶ is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,
- 20 Y is selected from O, S, NR²¹, C(R²²)-NO₂, C(R²²)-CN and C(CN)₂, wherein
- 25 R²¹ is independently selected from the meanings given for R¹³, R¹⁴ and
- R²² is independently selected from the meanings given for R¹¹, R¹²,
- p is independently in each case 0, 1, 2, 3, 4 or 5,
- 30 q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
- u is 0, 1, 2 or 3, preferably 0, 1 or 2,

103224 do.doc

13

and

Hal is independently selected from a group consisting of F, Cl,
5 Br and I;

the tautomeric forms thereof; and the pharmaceutically acceptable derivatives,
solvates, salts and stereoisomers thereof, including mixtures thereof in all
ratios, and more preferred the salts and/or solvates thereof, and especially
10 preferred the physiologically acceptable salts and/or solvates thereof.

As used herein, the term "effective amount" means that amount of a drug or
pharmaceutical agent that will elicit the biological or medical response of a
tissue, system, animal or human that is being sought, for instance, by a
15 researcher or clinician. Furthermore, the term "therapeutically effective
amount" means any amount which, as compared to a corresponding subject
who has not received such amount, results in improved treatment, healing,
prevention, or amelioration of a disease, disorder, or side effect, or a
decrease in the rate of advancement of a disease or disorder. The term also
20 includes within its scope amounts effective to enhance normal physiological
function.

As used herein, the term "alkyl" preferably refers to a straight or branched
chain hydrocarbon having from one to twelve carbon atoms, optionally
25 substituted with substituents selected from the group consisting of C₁-C₈
alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylsulfanyl, C₁-C₈ alkylsulfenyl, C₁-C₈
alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl,
carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally
substituted by alkyl, nitro, cyano, halogen, or C₁-C₈ perfluoroalkyl, multiple
30 degrees of substitution being allowed. Examples of "alkyl" as used herein
include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl,
isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

103224 do.doc

14

As used herein, the term "C₁-C₆ alkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms. Examples of branched or straight chained "C₁-C₆ alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 5 isobutyl, n-butyl, t-butyl, n-pentyl and isopentyl.

As used herein, the term "alkylene" preferably refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which 10 includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as 15 used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

As used herein, the term "C₁-C₆ alkylene" preferably refers to an alkylene group, as defined above, which contains at least 1, and at most 6, carbon 20 atoms respectively. Examples of "C₁-C₆ alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene and n-Propylene.

As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), 25 chlorine (Cl), bromine (Br) or iodine (I).

As used herein, the term "C₁-C₆ haloalkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halogen, halogen being as defined herein. 30 Examples of branched or straight chained "C₁-C₆ haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl,

103224 do.doc

15

isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

5 As used herein, the term "cycloalkyl" or "C₃-C₇ cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C₁-C₆ alkyl linker through which it may be attached. The C₁-C₆ alkyl group is as defined above. Exemplary "C₃-C₇ cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkyl", as used herein
10 preferably also includes saturated heterocyclic groups, which are preferably selected from the cycloalkyl-groups as defined above, wherein one or two carbon atoms are replaced by hetero atoms, selected from the group consisting of O, N and S, which optionally is substituted by one or more substituents, preferably selected from alkyl, =O, =S and substituted or
15 unsubstituted imino groups.

As used herein, the term "C₃-C₇ cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven carbon atoms, optionally substituted with substituents selected from the
20 group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of
25 "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" preferably
30 refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O or N, optionally substituted with substituents

103224 do.doc

16

selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ haloalkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C₁-C₆ perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO₂, O or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Exemplary optional substituents include C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally

I03224 do.doc

17

substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C₁-C₆ perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being
5 allowed. Examples of "aryl" groups include, but are not limited to Phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof. As used herein, the term "arylene" preferably refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents
10 selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano,
15 halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a C₁-C₆ alkyl linker, wherein C₁-C₆ alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolylethyl.

25 As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are
30 permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ haloalkylsulfanyl, C₁-C₆

103224 do.doc

18

alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C₁-C₆ perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five - to seven -membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" preferably refers to the group R_aO-, where R_a is alkyl as defined above and the term "C₁-C₆ alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least

103224 do.doc

19

1 and at most 6 carbon atoms. Exemplary C₁-C₆ alkoxy groups useful in the present invention include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy.

- 5 As used herein, the term "haloalkoxy" preferably refers to the group R_aO-, where R_a is haloalkyl as defined above and the term "C₁-C₆ haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary C₁-C₆ haloalkoxy groups useful in the present invention include, but are not
10 limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

As used herein the term "aralkoxy" preferably refers to the group R_CR_BO-, where R_B is alkyl and R_C is aryl as defined above.

15

As used herein the term "aryloxy" preferably refers to the group R_CO-, where R_C is aryl as defined above.

20

As used herein, the term "alkylsulfanyl" preferably refers to the group R_AS-, where R_A is alkyl as defined above and the term "C₁-C₆ alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

25

As used herein, the term "haloalkylsulfanyl" preferably refers to the group R_DS-, where R_D is haloalkyl as defined above and the term "C₁-C₆ haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

30

As used herein, the term "alkylsulfenyl" preferably refers to the group R_AS(O)-, where R_A is alkyl as defined above and the term "C₁-C₆

I03224 do.doc

20

alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

5 As used herein, the term "alkylsulfonyl" preferably refers to the group $R_A\text{SO}_2-$, where R_A is alkyl as defined above and the term "C₁-C₆ alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

10 As used herein, the term "oxo" preferably refers to the group =O.

As used herein, the term "mercapto" preferably refers to the group -SH.

As used herein, the term "carboxy" preferably refers to the group -COOH.

15 As used herein, the term "cyano" preferably refers to the group -CN.

20 As used herein, the term "cyanoalkyl" preferably refers to the group -R_BCN, wherein R_B is alkyl as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

As used herein, the term "aminosulfonyl" preferably refers to the group -SO₂NH₂.

25 As used herein, the term "carbamoyl" preferably refers to the group -C(O)NH₂.

As used herein, the term "sulfanyl" shall refer to the group -S-.

30 As used herein, the term "sulfenyl" shall refer to the group -S(O)-.

As used herein, the term "sulfonyl" shall refer to the group -S(O)₂- or -SO₂-.

103224 do.doc

21

As used herein, the term "acyl" preferably refers to the group $R_F C(O)-$, where R_F is alkyl, cycloalkyl or heterocyclyl as defined herein.

5 As used herein, the term "aroyl" preferably refers to the group $R_C C(O)-$, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyl" preferably refers to the group $R_E C(O)-$, where R_E is heteroaryl as defined herein.

10

As used herein, the term "alkoxycarbonyl" preferably refers to the group $R_A OC(O)-$, where R_A is alkyl as defined herein.

15 As used herein, the term "acyloxy" preferably refers to the group $R_F C(O)O-$, where R_F is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyloxy" preferably refers to the group $R_C C(O)O-$, where R_C is aryl as defined herein.

20 As used herein, the term "heteroaroyloxy" preferably refers to the group $R_E C(O)O-$, where R_E is heteroaryl as defined herein.

As used herein, the term "carbonyl" or "carbonyl moiety" preferably refers to the group $C=O$.

25

As used herein, the term "thiocarbonyl" or "thiocarbonyl moiety" preferably refers to the group $C=S$.

30 As used herein, the term "amino", "amino group" or "imino moiety" preferably refers to the group $NR_G R_{G'}$, wherein R_G and $R_{G'}$ are preferably selected, independently from one another, from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl,

103224 do.doc

22

aryl, aralkyl, heteroaryl, acyl and aroyl. If both R_G and $R_{G'}$ are hydrogen, $NR_G R_{G'}$ is also referred to as "unsubstituted amino moiety" or "unsubstituted amino group". If R_G and/or $R_{G'}$ are other than hydrogen, $NR_G R_{G'}$ is also referred to as "substituted amino moiety" or "substituted amino group".

5

As used herein, the term "imino" or "imino moiety" preferably refers to the group $C=NR_G$, wherein R_G is preferably selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If R_G is hydrogen, $C=NR_G$ is also referred to as "unsubstituted imino moiety". If R_G is a residue other than hydrogen, $C=NR_G$ is also referred to as "substituted imino moiety".

10

As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is common practice in the art.

15

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

20

As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

25

30

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I

103224 do.doc

23

or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent
5 used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "substituted" preferably refers to substitution with
10 the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more
15 stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also
20 included within the scope of the invention are the individual isomers of the compounds represented by formulae I above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral Centers are
25 inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formulae I are included within the scope of the compounds of formulae I and preferably the formulae and subformulae corresponding thereto.

30 Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent.

103224 do.doc

24

Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as β -camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenylglycine); an example of a suitable eluent is a hexane/isopropanol/ acetonitrile mixture.

10 The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

15 It is of course also possible to obtain optically active compounds of the formula I by the methods described above by using starting materials which are already optically active.

Unless indicated otherwise, it is to be understood that reference to compounds of formula I preferably includes the reference to the compounds of formula I' and I''. Unless indicated otherwise, it is to be understood that reference to the compounds of formula I, I' and I'' preferably includes the reference to the sub formulae corresponding thereto, for example the sub formulae I.1 to I.15 and preferably formulae Ia to Ir. It is also understood that the following embodiments, including uses and compositions, although recited with respect to formula I are preferably also applicable to formulae I', I'' and sub formulae I.1 to I.15 and preferably formulae Ia to Ir.

Even more preferred are compounds of formula I

wherein

30 Ar^1 is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical

103224 do.doc

25

unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

5

 R^8 , R^9 and R^{10}

are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, $\text{C}(\text{Hal})_3$, NO_2 , $(\text{CH}_2)_n\text{CN}$, OHet, $\text{N}(\text{R}^{11})\text{Het}$, $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} ,

10

$(\text{CR}^5\text{R}^6)_k\text{Het}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{Het}$, $\text{N}(\text{R}^{11})(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, and/or are

15

independently selected from a group consisting of $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} ,

$(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,

20

$(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, $(\text{CH}_2)_n\text{OC}(\text{O})\text{R}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{SR}^{11}$, $(\text{CH}_2)_n\text{NHOA}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OCF}_3$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOOR}^{12}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOOR}^{11}$, $(\text{CH}_2)_n\text{N}(\text{COOR}^{13})\text{COOR}^{14}$, $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{CONH}_2$, $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{COOR}^{13})\text{COOR}^{14}$, $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{CONH}_2$, $(\text{CH}_2)_n\text{CHR}^{13}\text{COR}^{14}$, $(\text{CH}_2)_n\text{CHR}^{13}\text{COOR}^{14}$ and $(\text{CH}_2)_n\text{CHR}^{13}\text{CH}_2\text{OR}^{14}$.

25

30

p

is 1, 2, 3 or 4, preferably 1, 2 or 3, and

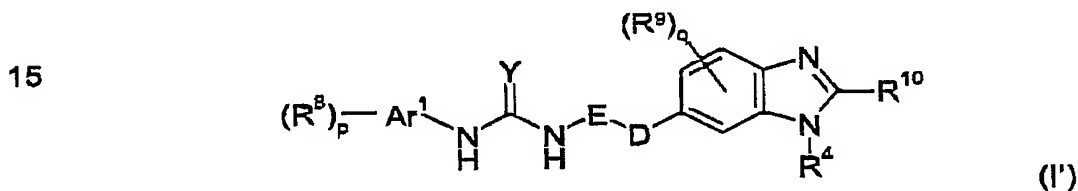
I03224 do.doc

26

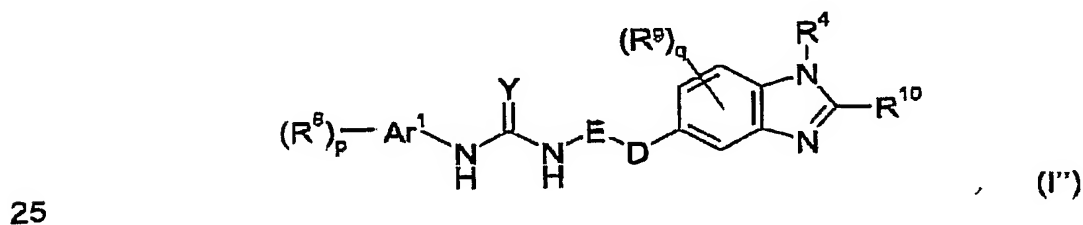
the tautomeric forms thereof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Subject of the present invention are especially compounds of formula I in which one or more substituents or groups, preferably the major part of the substituents or groups has a meaning which is indicated as preferred, more preferred, even more preferred or especially preferred.

More preferred compounds of formula I are compounds of formula I',



and/or compounds of formula I'',



25

wherein each residue R^8 , p , Ar^1 , Y , E , D , R^9 , R^4 , R^{10} and q are independently selected from the meanings given above/below. It is understood that if R^4 is Hydrogen (H) or any other group prone to dissociation, formulae I' and II' describe tautomeric forms of the same compound, which are usually in an equilibrium relation with one another and thus usually are inseparable. The equilibrium can be depending on various matters, such as the state of

30

I03224 de.doc

27

aggregation, the pH value, the solvent the compounds are diluted in etc. Hence, all tautomeric forms are subject of the present invention, no matter which one of the tautomeric forms is depicted in the respective formula.

5 In compounds of formula I, the term alkyl preferably refers to an unbranched or branched alkyl residue, preferably an unbranched alkyl residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or 6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a branched alkyl residue comprising 3, 4, 5, 6, 7, 8, 9 or 10, preferably 3, 4, 5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be optionally substituted, especially
10 by one or more halogen atoms, for example up to perhaloalkyl, by one or more hydroxy groups or by one or more amino groups, all of which can optionally be substituted by alkyl. If an alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5 halogen atoms, depending on the number
15 of carbon atoms of the alkyl residue. For example, a methyl group can comprise, 1, 2 or 3 halogen atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by hydroxy groups, it usually comprises one or two, preferably one hydroxy groups. If the hydroxy group is substituted by
20 alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon
25 atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. According to compounds of formula I, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-
30 2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further preferred of the group consisting of 2-butyl, n-pentyl, neo-pentyl, isopentyl,

103224 do.doc

28

hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isopropyl and tert.-butyl.

5 In compounds of formula I, alkenyl is preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

10 In compounds of formula I, alkylene is preferably unbranched and is more preferably methylene or ethylene, furthermore preferably propylene or butylene.

15 In compounds of formula I, alkylencycloalkyl preferably has 5 to 10 carbon atoms and is preferably methylenecyclopropyl, methylenecyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or ethylenecycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.

20 In compounds of formula I, the term "alkoxy" preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group as defined above. More preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives
25 are selected from the group consisting of O-CCl₃, O-CF₃, O-C₂Cl₅, O-C₂F₅, O-C(CCl₃)₃ and O-C(CF₃)₃.

30 In compounds of formula I, the term "alkoxyalkyl" preferably comprises branched and unbranched residues, more preferred unbranched residues, of formula C_uH_{2u+1}-O-(CH₂)_v, wherein u and v are independently from each other 1 to 6. Especially preferred is u = 1 and v 1 to 4.

I03224 do.doc

29

In compounds of formula I the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

5 In compounds of formula I, cycloalkyl preferably has 3 – 7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl. The term "cycloalkyl", as used herein preferably also includes saturated heterocyclic groups, wherein one or two carbon atoms are substituted by
10 hetero atoms, selected from the group consisting of O, NH, NA and S, wherein A is as defined as above/below. Cycloalkyl residues as defined herein can optionally be substituted, the substituents preferably selected from A, R¹³, =O, =S, =N-R¹⁴, CN and hal.

15 In compounds of formula I, Ar³ to Ar⁶ are preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally substituted by one or more substituents, selected from the group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵.

20

In compounds of formula I, Het is preferably an optionally substituted aromatic heterocyclic residue and even more preferred an optionally substituted saturated heterocyclic residue. In substituted saturated heterocyclic residues, the substituents are preferably selected from A, R¹³,
25 =O, =S, =N-R¹⁴, CN and hal. Even more preferred, Het is selected from the group consisting of 1-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-hydroxyethyl))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, quinolinyl, isoquinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl,

30

I03224 do.doc

30

5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl. Further preferred, Het as defined above is optionally substituted by one or more substituents preferably selected from A, R^{13} , =O, =S, =N- R^{14} , CN and hal. More preferred, Het is either unsubstituted or substituted once or twice by =O.

5

In compounds of formula I, saturated heterocyclyl is preferably a substituted or unsubstituted saturated heterocyclic residue, more preferred an unsubstituted saturated heterocyclic residue, preferably selected from the saturated groups given above in the definition of Het. Further preferred,

10

saturated heterocyclyl as defined above is optionally substituted by one or more substituents preferably selected from A, R^{13} , =O, =S, =N- R^{14} , CN and hal. More preferred, saturated heterocyclyl is either unsubstituted or substituted once or twice by =O.

15

In compounds of formula I, aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S, are preferably selected from the definitions given herein for aryl, heteroaryl and/or Het. Heteroaryl is more preferably furanyl,

20

thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinoliny, isoquinoliny, benzofuranyl, benzothiophenyl, indolyl, indazolyl and even more preferably pyridinyl, pyrimidyl, quinoliny, isoquinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl,

25

oxazolyl, isoxazolyl, pyrazolyl and/or imidazolyl. Aryl more preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Even more preferably, aryl is selected from the group consisting of

30

phenyl, 2-naphthyl, 1-naphthyl, biphenyl.

103224 do.doc

31

In compounds of formula I, Ar^1 is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, and especially from phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl and oxazolyl. Especially preferred, Ar^1 is phenyl or pyridinyl.

In compounds of formula I, $(CR^5R^6)_n$ and $(CR^5R^6)_k$ preferably form a linear or branched alkylene residue, preferably linear or branched C_1 - C_4 alkylene residue, which is optionally substituted as described above/below and preferably is unsubstituted.

In compounds of formula I, A and D preferably both are CR^5R^6 , respectively. Accordingly, A and D preferably form a linear or branched alkylene residue, more preferably linear or branched C_1 - C_4 alkylene residue, which is optionally substituted as described above/below and preferably is unsubstituted.

Preferably, the sum of h and i in one residue exceeds 0.

Preferably, the sum of n and k in one residue exceeds 0.

Another preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 in the residues R^8 , R^9 and/or R^{10} and especially in R^{10} .

The invention relates in particular to compounds of the formula I in which at least one of said radicals has one of the preferred meanings given above/below.

Some more preferred groups of compounds may be expressed by the following sub-formulae I.1) to I.15), which correspond to the formula I and in

103224 do.doc

32

which radicals not denoted in greater detail are as defined in the formula I,
but in which

- 5 1.1) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinoliny, isoquinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinoliny, isoquinoliny, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl;
- 10 1.2) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinoliny, isoquinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinoliny, isoquinoliny, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl, and
- 15
- p is 1, 2 or 3;
- 20 1.3) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinoliny, isoquinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinoliny, isoquinoliny, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 25
- p is 1, 2 or 3, and
- 30 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,

I03224 do.doc

33

5
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$,
 $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$,
 $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^1$ and/or OHet,
 $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$,
 $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$,
 $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$,
 $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$;

10 1.4) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl,
thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl,
isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl,
pyridinyl, quinolinyl, isoquinolinyl, thiophenyl,
15 benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even
more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

20 R^8 is selected from the group consisting of alkyl comprising 1
to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4
carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$,
25 $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$,
 $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$ and/or OHet,
 $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$,
 $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$,
 $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$,
30 $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$,
wherein

103224 do.doc

34

- n is 0 or 1;
- 5 1.5) Ar¹ is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 10 p is 1, 2 or 3,
- 15 R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uR¹³ and/or OHet, N(R¹¹)Het, (CR⁵R⁶)_kHet, O(CR⁵R⁶)_kHet, N(R¹¹)(CR⁵R⁶)_kHet, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³, O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, wherein
- 25 n is 0 or 1, and
- k is 1 or 2;
- 30 1.6) Ar¹ is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl,

103224 do.doc

35

pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl.

- 5 p is 1, 2 or 3,
- R⁶ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³ and/or OHet, N(R¹¹)Het, (CR⁵R⁶)_kHet, O(CR⁵R⁶)_kHet, N(R¹¹)(CR⁵R⁶)_kHet, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³, O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, wherein
- 10 n is 0 or 1,
- k is 1 or 2, and
- 15 u is 0;
- 20 1.7) Ar¹ is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, quinolinyl, isoquinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl.
- 25 30

103224 do.doc

36

p is 1, 2 or 3,

5 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$,
10
15 wherein

n is 0 or 1,

20 k is 1 or 2,

u is 0,

25 q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $CHAl_3$, perhaloalkyl comprising 2 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$,
30

103224 do.doc

37

- $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$,
 $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$,
 $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
5 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$,
 $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and
 $(CH_2)_nS(O)_4R^{13}$, more preferably selected from alkyl
comprising 1 to 4 carbon atoms, $(CH_2)_nCN$, CH_2Hal ,
10 $CH(Hal)_2$, $CHal_3$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$,
 $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$,
 $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$,
 $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$,
15 $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$,
 $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$,
 $(CH_2)_nNR^{11}COOR^{13}$,
- 20 1.8) Ar^1 is phenyl, pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl,
thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl,
isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl,
pyridinyl, quinolinyl, isoquinolinyl, thiophenyl,
benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even
25 more preferably phenyl or pyridinyl,
- p is 1, 2 or 3,
- 30 R^8 is selected from the group consisting of alkyl comprising 1
to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4
carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,

103224 do.doc

38

5 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³,
 (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³
 and/or OHet, N(R¹¹)Het, (CR⁵R⁶)_kHet, O(CR⁵R⁶)_kHet,
 N(R¹¹)(CR⁵R⁶)_kHet, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³,
 O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³,
 NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³,
 wherein

10 n is 0 or 1,

k is 1 or 2,

u is 0,

15 q is 0 or 1, and

20 R¹⁰ is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4
 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, CHal₃, perhaloalkyl
 comprising 2 to 4 carbon atoms, NO₂, (CH₂)_nCN,
 NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³,
 NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kNR¹¹R¹²,
 NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, (CR⁵R⁶)_kNR¹¹R¹²,
 (CR⁵R⁶)_kHet, (CR⁵R⁶)_kOR¹³, (CH₂)_nNR¹¹R¹²,
 25 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹,
 (CH₂)_nCOOR¹³, (CH₂)_nCOR¹³,
 (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³,
 (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nCOR¹³,
 (CH₂)_nNR¹¹COOR¹³, (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹²,
 30 (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nSO₂NR¹¹R¹² and
 (CH₂)_nS(O)_uR¹³, more preferably selected from alkyl
 comprising 1 to 4 carbon atoms, (CH₂)_nCN, CH₂Hal,

103224 do.doc

39

- CH(Hal)₂, CHHal₃, NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹²,
 COOR¹³, NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kNR¹¹R¹²,
 NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, (CR⁵R⁶)_kNR¹¹R¹²,
 (CR⁵R⁶)_kHet, (CR⁵R⁶)_kOR¹³, (CH₂)_nNR¹¹R¹²,
 5 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹,
 (CH₂)_nCOOR¹³, (CH₂)_nCOR¹³,
 (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³,
 (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nCOR¹³,
 (CH₂)_nNR¹¹COOR¹³, wherein
 10 n is 0, 1 or 2, preferably 0 or 1;
 1.9) p is 1, 2 or 3,
 15 R⁸ is selected from the group consisting of alkyl comprising 1
 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
 Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4
 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹²,
 20 (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³ and/or OHet,
 N(R¹¹)Het, (CR⁵R⁶)_kHet, O(CR⁵R⁶)_kHet,
 N(R¹¹)(CR⁵R⁶)_kHet, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³,
 25 O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³,
 NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³,
 wherein
 30 n is 0 or 1,
 k is 1 or 2.

103224 do.doc

40

u is 0,

q is 0 or 1,

5 R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $CHAl_3$, perhaloalkyl comprising 2 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, more preferably selected from alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nCN$, CH_2Hal , $CH(Hal)_2$, $CHAl_3$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$, $(CH_2)_nNR^{11}COOR^{13}$, wherein

30 n is 0, 1 or 2, preferably 0 or 1:

**Fax**

An Europäisches Patentamt
 80298 München

Von Merck Patent GmbH
 Patents Pharmaceuticals
 Dr. Dotzauer

E-Mail patent@merck.de

Telefon +49 (0) 6151 72-4371

Fax +49 (0) 6151 72-7191

Datum 26.02.2004

Fax +49 89 2399 4465
Seiten 51

Antrag auf Erteilung eines europäischen Patents vom 26.02.2004

Zeichen des Anmelders: 103224-do/ki

Titel: „Benzimidazolyl derivatives“

Teil 2: Fax (1 Seite)
 Anmeldung (Seite 41-90)

103224 do.doc

41

- 5 I.10) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein
- 15 n is 0 or 1,
- k is 1 or 2,
- u is 0,
- 20 q is 0 or 1,
- R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $CHal_3$, perhaloalkyl comprising 2 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$,
- 25
- 30

$(CH_2)_nCONR^{11}R^{12}, (CH_2)_nNR^{11}COR^{13},$
 $(CH_2)_nNR^{11}CONR^{11}R^{12}, (CH_2)_nNR^{11}SO_2A, (CH_2)_nCOR^{13},$
 $(CH_2)_nNR^{11}COOR^{13}, (CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12},$
 $(CH_2)_nNR^{11}(CH_2)_kOR^{12}, (CH_2)_nSO_2NR^{11}R^{12}$ and
 $(CH_2)_nS(O)_uR^{13},$ more preferably selected from alkyl
 comprising 1 to 4 carbon atoms, $(CH_2)_nCN, CH_2Hal,$
 $CH(Hal)_2, CHal_3, NR^{11}COR^{13}, NR^{11}COOR^{13}, CONR^{11}R^{12},$
 $COOR^{13}, NR^{11}(CR^5R^6)_kR^{13}, NR^{11}(CR^5R^6)_kNR^{11}R^{12},$
 $NR^{11}(CR^5R^6)_kR^{13}, NR^{11}(CR^5R^6)_kOR^{13}, (CR^5R^6)_kNR^{11}R^{12},$
 $(CR^5R^6)_kHet, (CR^5R^6)_kOR^{13}, (CH_2)_nNR^{11}R^{12},$
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}, (CH_2)_nO(CH_2)_kOR^{11},$
 $(CH_2)_nCOOR^{13}, (CH_2)_nCOR^{13},$
 $(CH_2)_nCONR^{11}R^{12}, (CH_2)_nNR^{11}COR^{13},$
 $(CH_2)_nNR^{11}CONR^{11}R^{12}, (CH_2)_nNR^{11}SO_2A, (CH_2)_nCOR^{13},$
 $(CH_2)_nNR^{11}COOR^{13},$

n is 0, 1 or 2, preferably 0 or 1;

I.11) R^8 is selected from the group consisting of alkyl comprising 1
 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
 Hal, $CH_2Hal, CH(Hal)_2,$ perhaloalkyl comprising 1 to 4
 carbon atoms, $NO_2, (CH_2)_nCN, (CH_2)_nNR^{11}R^{12},$
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}, (CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12},$
 $(CH_2)_nO(CH_2)_kOR^{11}, (CH_2)_nNR^{11}(CH_2)_kOR^{12},$
 $(CH_2)_nCOR^{13}, (CH_2)_nCOOR^{13}, (CH_2)_nCONR^{11}R^{12},$
 $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet,
 $N(R^{11})Het, (CR^5R^6)_kHet, O(CR^5R^6)_kHet,$
 $N(R^{11})(CR^5R^6)_kHet, (CR^5R^6)_kNR^{11}R^{12}, (CR^5R^6)_kOR^{13},$
 $O(CR^5R^6)_kNR^{11}R^{12}, NR^{11}(CR^5R^6)_kNR^{11}R^{12}, O(CR^5R^6)_kR^{13},$
 $NR^{11}(CR^5R^6)_kR^{13}, O(CR^5R^6)_kOR^{13}, NR^{11}(CR^5R^6)_kOR^{13},$
 wherein

103224 do.doc

43

u is 0, and

q is 0 or 1, and

5 R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $CHal_3$, perhaloalkyl comprising 2 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$,
 10 $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
 15 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, more preferably selected from alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nCN$, CH_2Hal , $CH(Hal)_2$, $CHal_3$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$, $(CH_2)_nNR^{11}COOR^{13}$, $O(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

20
 25
 30

n is 0, 1 or 2, preferably 0 or 1;

1.12) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ and/or OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

q is 0 or 1, and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $CHal_3$, perhaloalkyl comprising 2 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and

103224 do.doc

45

5

10

n

15

I.13)

q

20

25

30

$(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, more preferably selected from alkyl
 comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{CN}$, CH_2Hal ,
 $\text{CH}(\text{Hal})_2$, CHal_3 , $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$,
 COOR^{13} , $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, wherein

is 0, 1 or 2, preferably 0 or 1;

is 0 or 1, and

 R^{10}

is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4
 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, CHal_3 , perhaloalkyl
 comprising 2 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$,
 $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} ,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and
 $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, more preferably selected from alkyl
 comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{CN}$, CH_2Hal ,

103224 do.doc

46

5

CH(Hal)₂, CHal₃, NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹²,
 COOR¹³, NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kNR¹¹R¹²,
 NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, (CR⁵R⁶)_kNR¹¹R¹²,
 (CR⁵R⁶)_kHet, (CR⁵R⁶)_kOR¹³, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹³,
 (CH₂)_nCOOR¹³, (CH₂)_nCOR¹³,
 (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³,
 (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nCOR¹³,
 (CH₂)_nNR¹¹COOR¹³, wherein

10

n is 0, 1 or 2, preferably 0 or 1;

I.14) R¹⁰

15

is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4
 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, CHal₃, perhaloalkyl
 comprising 2 to 4 carbon atoms, NO₂, (CH₂)_nCN,
 NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³,
 NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kNR¹¹R¹²,
 NR¹¹(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, (CR⁵R⁶)_kNR¹¹R¹²,
 (CR⁵R⁶)_kHet, (CR⁵R⁶)_kOR¹³, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹³,
 (CH₂)_nCOOR¹³, (CH₂)_nCOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nNR¹¹COR¹³, (CH₂)_nNR¹¹CONR¹¹R¹²,
 (CH₂)_nNR¹¹SO₂A, (CH₂)_nCOR¹³, (CH₂)_nNR¹¹COOR¹³,
 (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kOR¹³,
 (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, more preferably
 selected from alkyl comprising 1 to 4 carbon atoms,
 (CH₂)_nCN, CH₂Hal, CH(Hal)₂, CHal₃, NR¹¹COR¹³,
 NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³, NR¹¹(CR⁵R⁶)_kR¹³,
 NR¹¹(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kR¹³,
 NR¹¹(CR⁵R⁶)_kOR¹³, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kHet,
 (CR⁵R⁶)_kOR¹³, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹²,

20

25

30

$(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, wherein

5

n is 0, 1 or 2, preferably 0 or 1;

l.15) R^{10}

10

15

20

25

30

is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4
 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, CHal_3 , perhaloalkyl
 comprising 2 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$,
 $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} ,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and
 $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, more preferably selected from alkyl
 comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{CN}$, CH_2Hal ,
 $\text{CH}(\text{Hal})_2$, CHal_3 , $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$,
 COOR^{13} , $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$,

103224 do.doc

48

One preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein p is 1, 2 or 3 and R⁸ is independently selected from the group consisting of methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br, CF₃, C(CF₃)₃, SO₂CF₃, methoxy, ethoxy, tert.-butoxy, perfluoro tert.-butoxy (OC(CF₃)₃), methyl sulfanyl (SCH₃), ethyl sulfanyl (SCH₂CH₃), acetyl (COCH₃), propionyl (COCH₂CH₃), butyryl (COCH₂CH₂CH₃). If p is 2 or 3, all substituents can be the same or different.

10

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Y is selected from the group consisting of C(R²²)-NO₂, C(R²²)-CN and C(CN)₂.

15

Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Y is selected from the group consisting of O, S and NR²¹.

20

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Y is selected from the group consisting of O and S.

25

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Y is O.

30

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar¹ is phenyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar^1 comprises two or more substituents R^8 , wherein one or more, preferably one substituent R^8 is selected from the group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this embodiment, one or two substituents R^8 and preferably one substituent R^8 is especially preferably selected from the group consisting of NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3 , SC_2H_5 , SO_2CH_3 , $COOCH_3$ and $COOH$. Accordingly, in this embodiment Ar^1 especially preferably comprises at least one substituent R^8 other than $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ as defined in this paragraph and especially other than NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3 , SC_2H_5 , SO_2CH_3 , $COOCH_3$ and $COOH$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar^1 comprises two or more substituents R^8 , wherein one or more, preferably one substituent R^8 is selected from the group consisting of $OHet$, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$ and $NR^{11}(CR^5R^6)_kOR^{13}$, wherein R^{11} , R^{12} , R^{13} and Het are defined as above/below and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2.

In this embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this embodiment, one or two substituents R^8 and preferably one substituent R^8 is especially preferably selected from the group consisting of

5 OHet, OCH_2CH_2Het , $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$, $NHC(CH_3)CH_2NH_2$, $OC(CH_3)CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$ and $N(CH_3)CH_2CH_2OCH_3$. Accordingly, in this

embodiment Ar^1 especially preferably comprises at least one substituent R^8

10 other than OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$ and $NR^{11}(CR^5R^6)_kOR^{13}$ as defined in this paragraph and especially other than OHet, OCH_2CH_2Het , $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$,

15 $NHC(CH_3)CH_2NH_2$, $OC(CH_3)CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$ and $N(CH_3)CH_2CH_2OCH_3$.

Another preferred embodiment of the instant invention relates to compounds

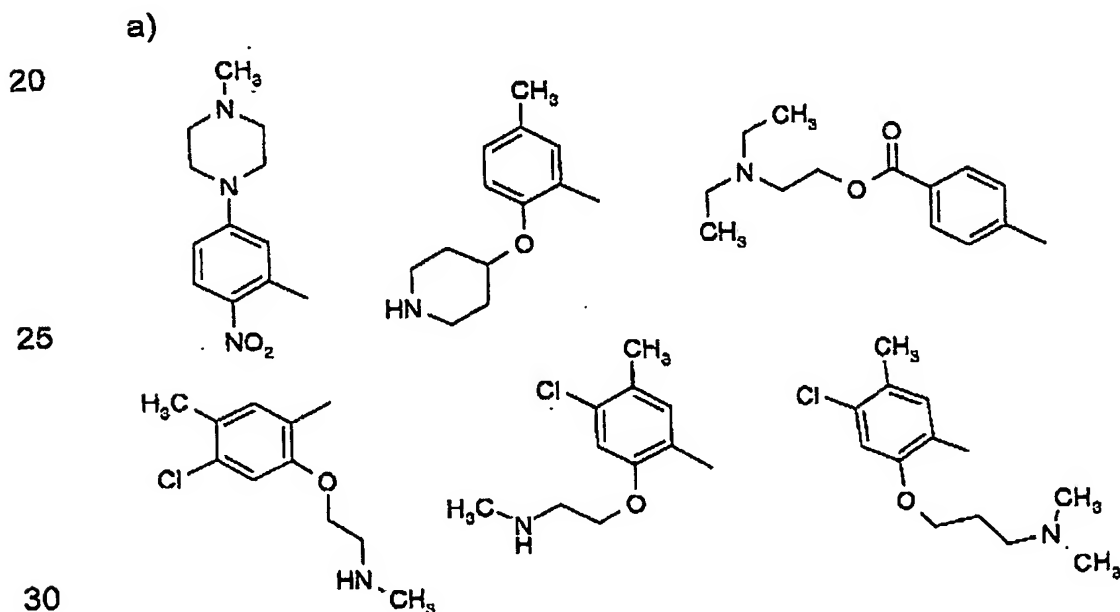
20 of formula I and preferably one or more of formulae I.1) to I.15), wherein $(R^8)_p-Ar^1$ is selected from the group consisting of 3-acetyl-phenyl, 4-acetyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-bromo-2-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-bromo-3-trifluoromethyl-phenyl, 2-chloro-phenyl, 2-chloro-4-trifluoromethyl-phenyl, 2-chloro-5-trifluoromethyl-phenyl,

25 3-chloro-phenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-chloro-phenyl, 4-chloro-2-trifluoromethyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 5-chloro-2-methoxy-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichloro-phenyl, 3,4-dichloro-phenyl, 3,5-dichloro-phenyl, 2,4,5-

30 trichloro-phenyl, 4-fluoro-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-ethoxy-phenyl, 2-methoxy-phenyl, 2-methoxy-5-trifluoromethyl-phenyl, 4-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-

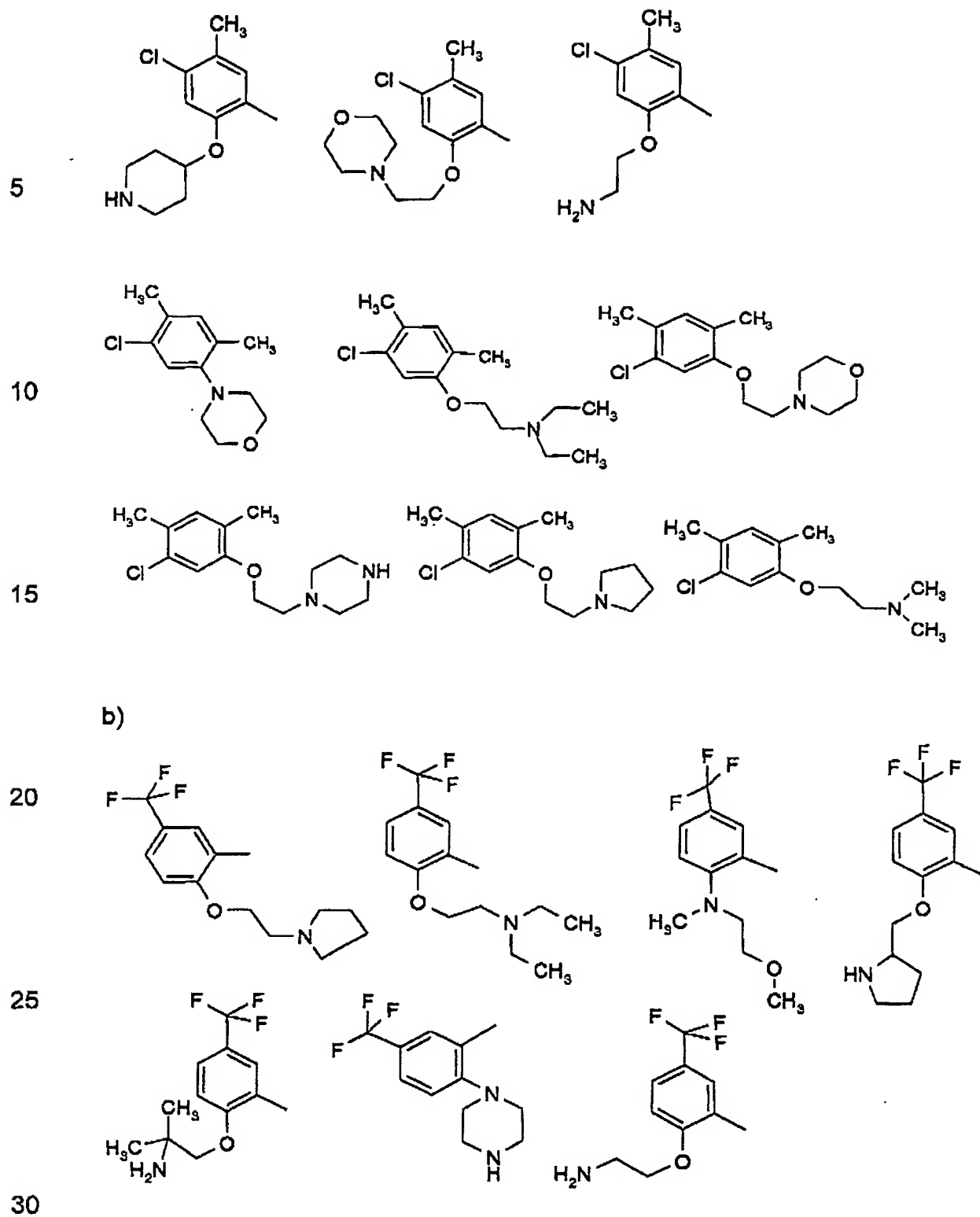
phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 3-methoxy-phenyl, 3-methylsulfanyl-phenyl, 4-methylsulfanyl-phenyl, o-tolyl (2-methyl-phenyl), m-tolyl (3-methyl-phenyl), p-tolyl (4-methyl-phenyl), 2,3-dimethyl-phenyl, 2,3-dimethyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 4-isopropyl-phenyl, 4-tert-butyl-phenyl and 5-tert-butyl-isoxazol-3-yl. Additionally preferred are compounds of formula I and preferably one or more of formulae I.1) to I.15), wherein $(R^8)_p\text{-Ar}^1$ is selected from the the residues given above, that additionally comprise one or two, preferably one additional substituent $(R^8)_p$ and especially one or two, preferably one additional substituent $(R^8)_p$ indicated herein as preferred, more preferred or especially preferred.

Another preferred embodiment of the instant invention relates to compounds of formula I and the subformulae related thereto and preferably one or more of formulae I.1) to I.15), wherein the residues $(R^8)_p\text{-Ar}^1$ are selected from the group consisting of the following formulae:



103224 do.doc

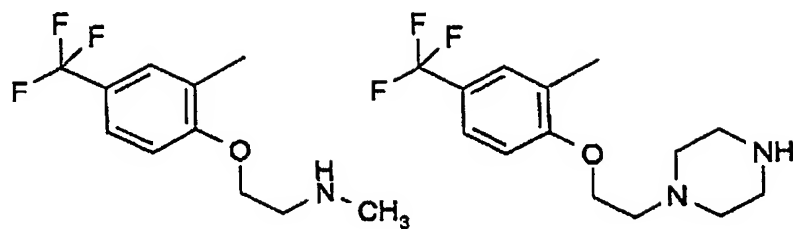
52



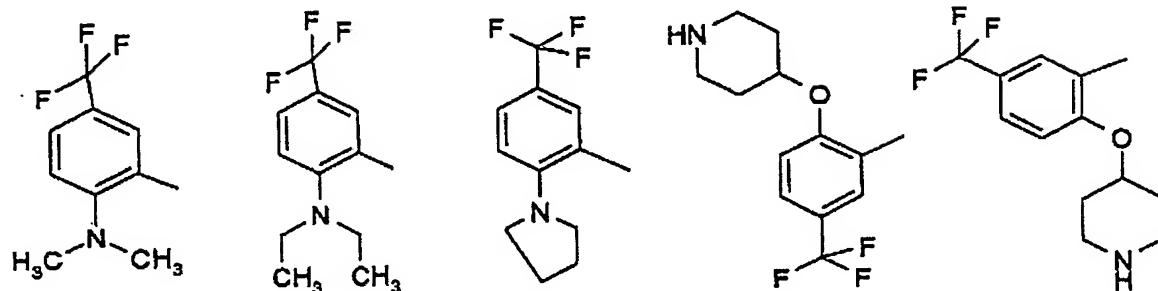
103224 do.doc

53

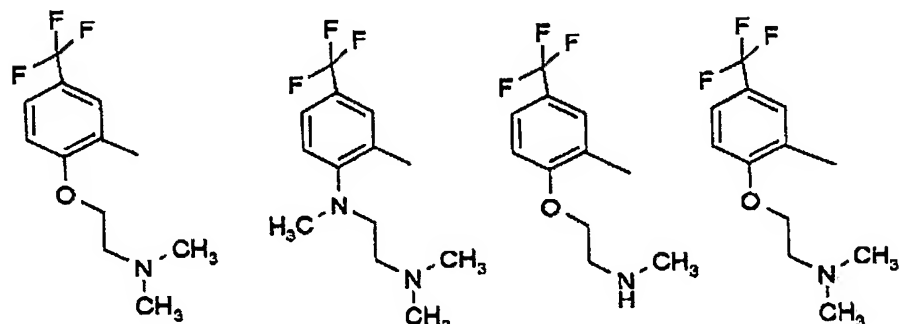
5



10



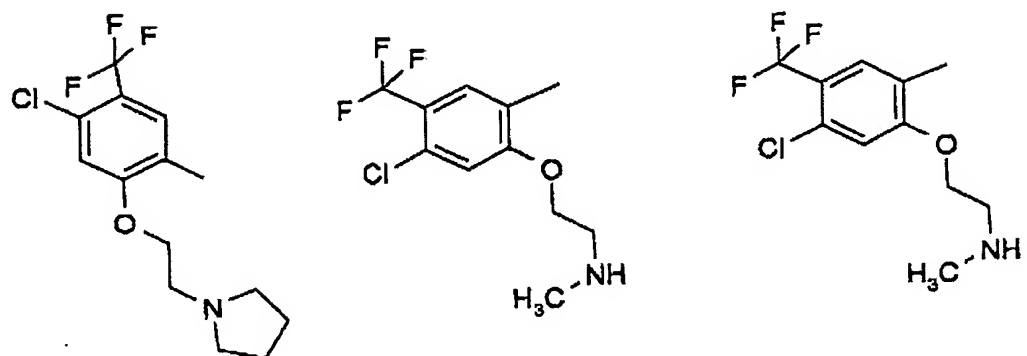
15



20

c)

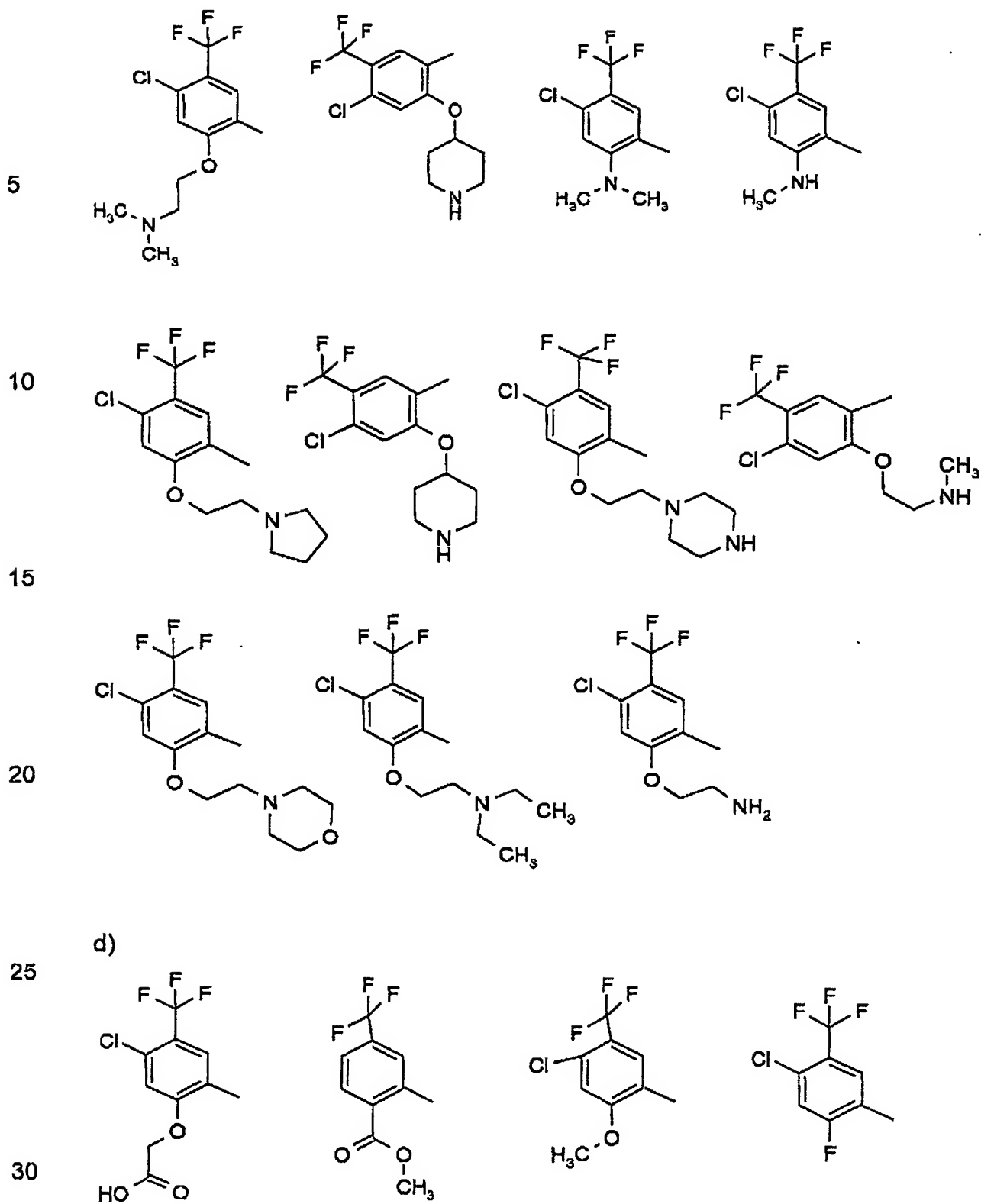
25



30

103224 do.doc

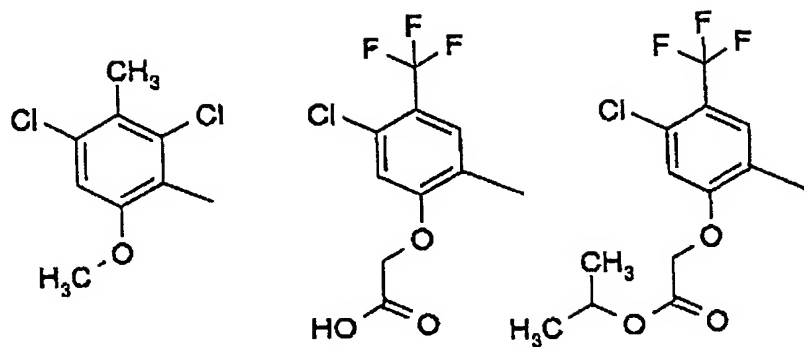
54



103224 do.doc

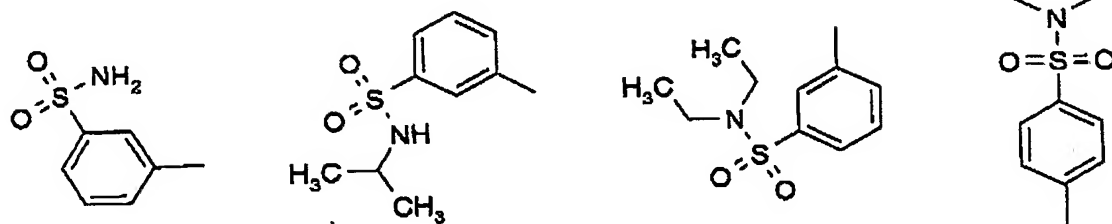
55

5



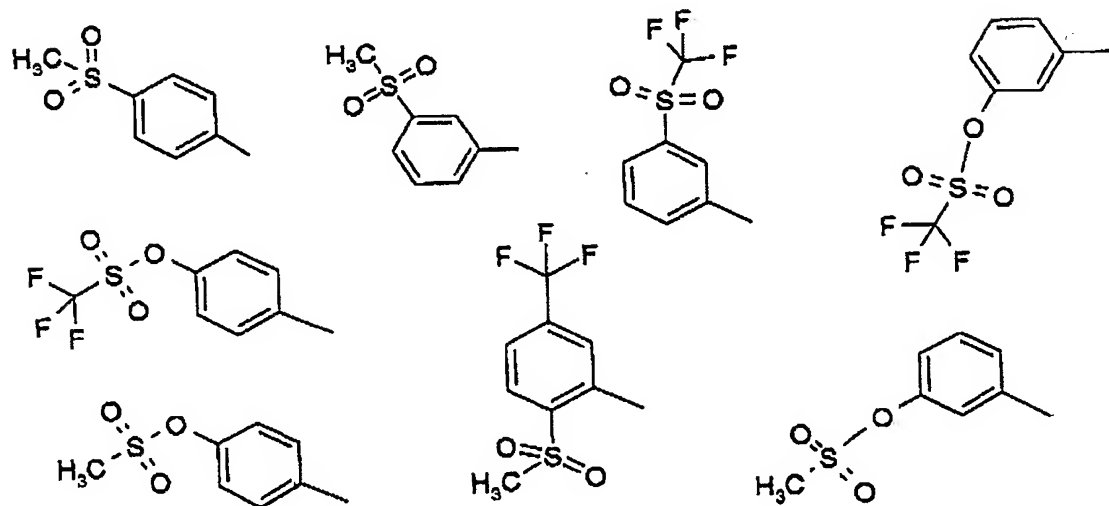
e)

10



15

20



25

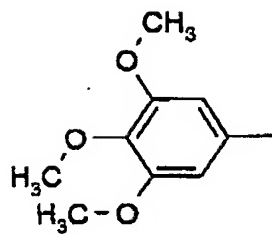
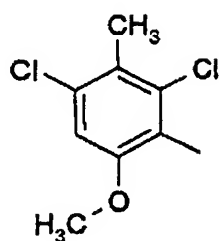
30

103224 do.doc

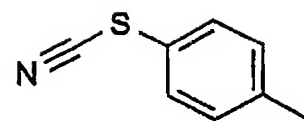
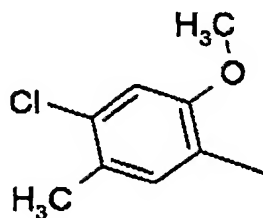
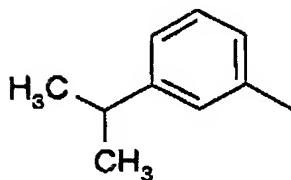
56

f)

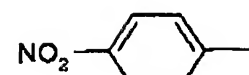
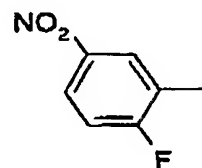
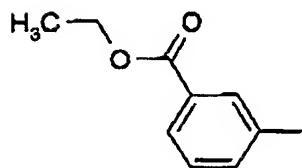
5



10

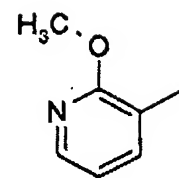
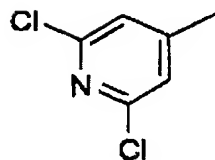
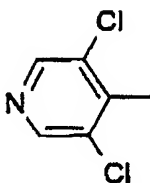
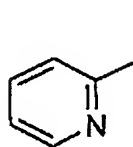


15

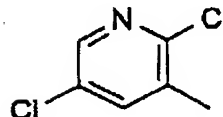
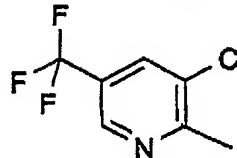
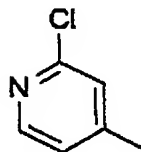


and/or

20

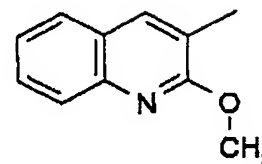
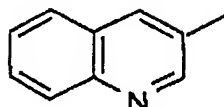
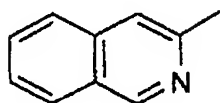


25



and/or

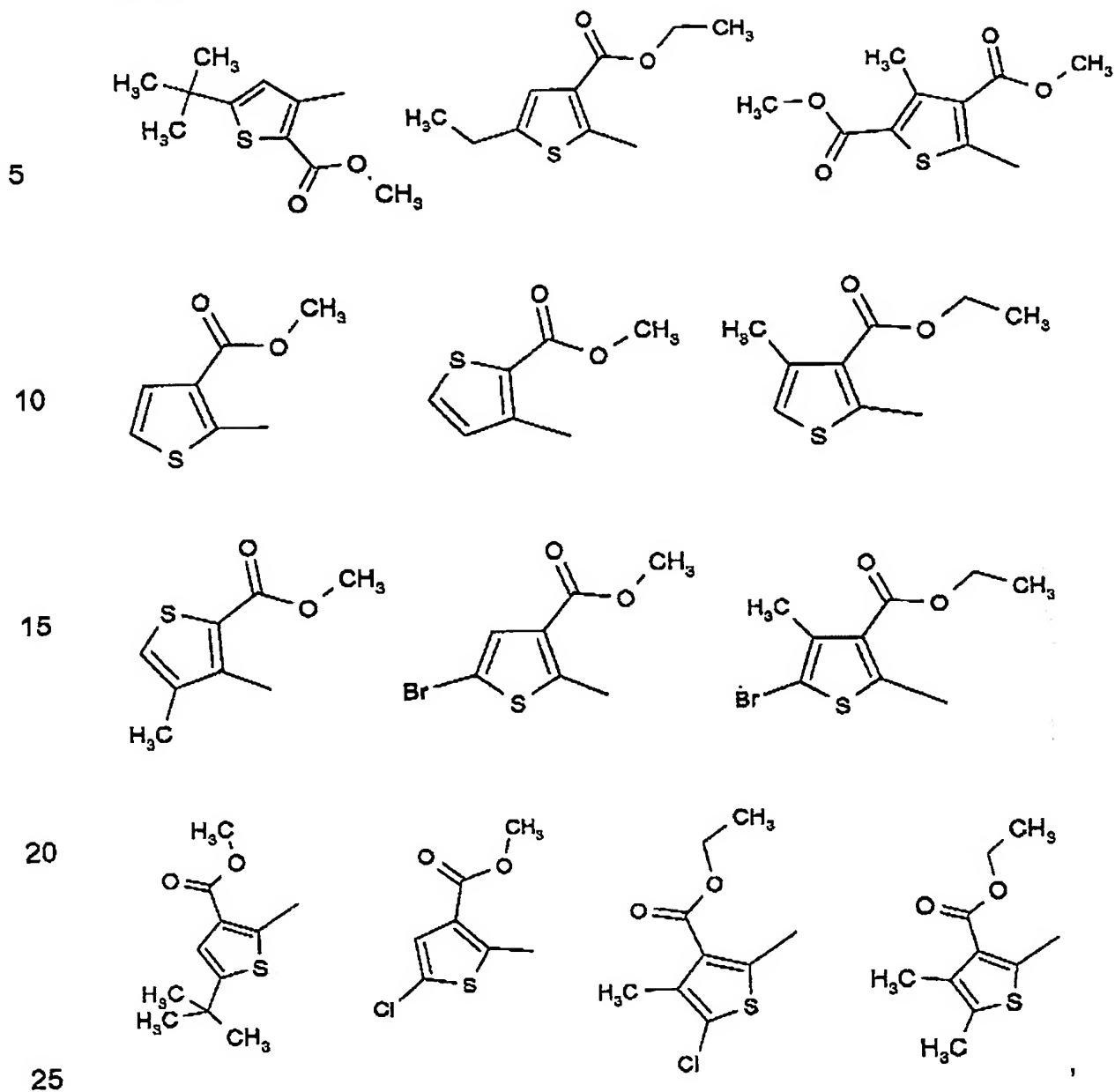
30



103224 do.doc

57

and/or



and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R⁸.

30

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein

$(R^8)_p-Ar^1$ is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^8 and more preferably selected from the group consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$,
 5 $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$,
 $(CH_2)_nS(O)_uNR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this
 10 embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$,
 $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$,
 15 $OCH_2CH_2N(CH_3)_2$, SC_2H_5 , SO_2CH_3 , SO_2CF_3 , OSO_2CH_3 , OSO_2CF_3 ,
 SO_2NH_2 , $SO_2NHCH(CH_3)_2$, $SO_2N(CH_3)_2$, $SO_2N(CH_2CH_3)_2$, 4-Morpholine-4-sulfonyl, $COOCH_3$ and $COOH$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein
 20 $(R^8)_p-Ar^1$ is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^8 and more preferably selected from the group consisting of $OHet$, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$,
 $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$,
 25 $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$ and
 $NR^{11}(CR^5R^6)_kOR^{13}$, wherein R^{11} , R^{12} , R^{13} and Het are defined as above/below and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2. In this embodiment R^{11} , R^{12}
 and R^{13} are more preferably selected independently from each other from the
 30 group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of $OHet$, OCH_2CH_2Het ,
 $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$,

$\text{NHC}(\text{CH}_3)\text{CH}_2\text{NH}_2$, $\text{OC}(\text{CH}_3)\text{CH}_2\text{NH}_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{NH}_2$,
 $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$,
 $\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ and $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$

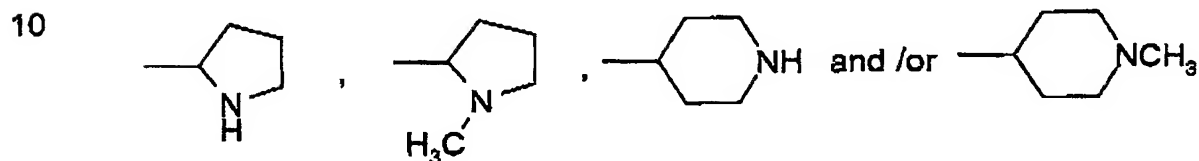
- 5 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar^1 comprises two or more substituents R^8 , wherein one or more, preferably one substituent R^8 comprises a group $\text{NR}^{11}\text{R}^{12}$, wherein R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered
- 10 heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, which optionally is substituted by one or more substituent, selected from A, R^{13} , $=\text{O}$, $=\text{S}$ and $=\text{N}-\text{R}^{14}$. In this embodiment, the heterocyclus is preferably selected from morpholine, piperazine, piperidine, pyrrolidine, especially from 1-piperidyl, 4-piperidyl, 1-methyl-
- 15 piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-hydroxyethyl))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, and/or oxomorpholine, oxopiperazine, oxopiperidine and oxopyrrolidine. More preferably, the oxo substituted heterocyclus is selected from 2-oxo-piperidin-1-yl, 2-oxo-piperidin-4-yl, 1-methyl-2-oxo-piperidin-4-yl,
- 20 2-oxo-piperazin-1-yl, 4-methyl-2-oxo-piperazin-1-yl, 4-methyl-2-oxo-piperazin-1-yl amine, 4-(2-hydroxyethyl)-2-oxo-piperazin-1-yl, 3-oxo-morpholin-4-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-5-yl and/or 3-oxo-piperidin-1-yl, 3-oxo-piperidin-4-yl, 1-methyl-3-oxo-piperidin-4-yl, 3-oxo-piperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl
- 25 amine, 4-(2-hydroxyethyl)-3-oxo-piperazin-1-yl, 2-oxo-morpholin-4-yl, 3-oxo-pyrrolidin-1-yl, 4-oxo-pyrrolidin-3-yl.

- Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein
- 30 Ar^1 comprises two or more substituents R^8 , wherein one or more, preferably one substituent R^8 comprises a terminal group R^{11} , R^{12} , R^{13} or R^{14} , preferably a group R^{13} , that is selected from cycloalkyl and Het, more

103224 do.doc

60

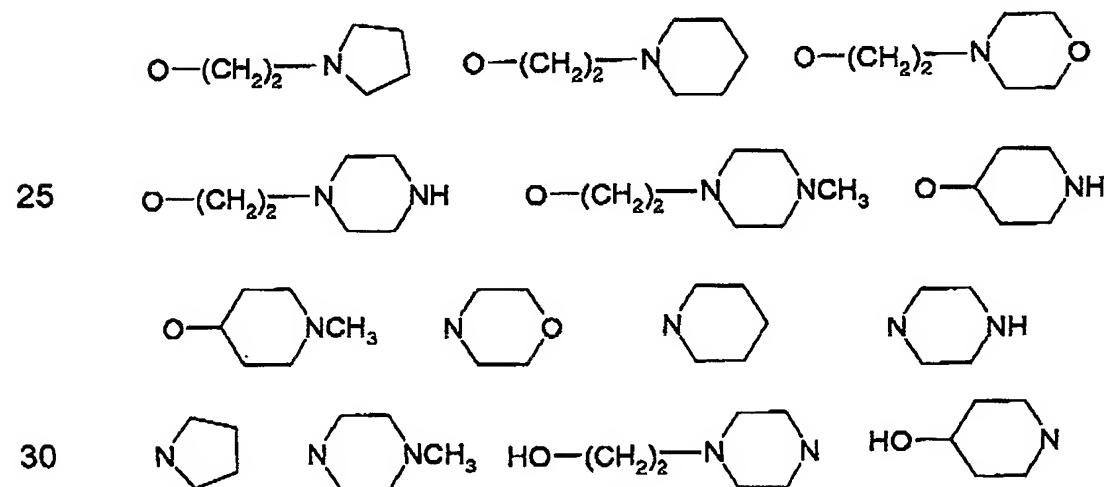
preferred from cycloalkyl and saturated heterocyclyl and especially from saturated heterocyclyl. In this embodiment, saturated heterocycl is preferably selected from 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-methyl-piperidin-3-yl, 1-methyl-piperidin-2-yl, 2-piperazyl, 3-piperazyl, 2-(4-methyl)-piperazyl, 3-(4-methyl)-piperazyl, 4-methylpiperazin-2-yl amine, 4-methylpiperazin-3-yl amine, 2-(4-(2-hydroxyethyl))-piperazyl, 3-(4-(2-hydroxyethyl))-piperazyl, 3-morpholinyl, 2-morpholinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, and and especially from



15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae 1.1) to 1.15), wherein Ar^1 comprises two or more substituents R^8 as defined above/below; wherein one or two, preferably one substituent R^8 is selected from the group consisting of residues of formulae aa):

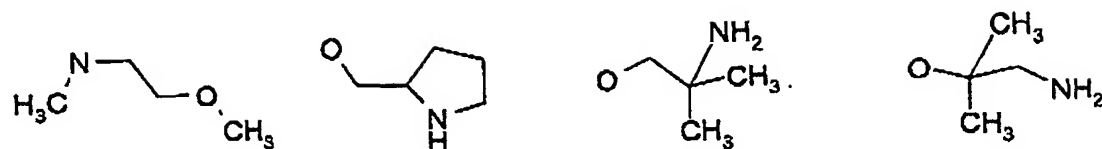
20

aa)



103224 do.doc

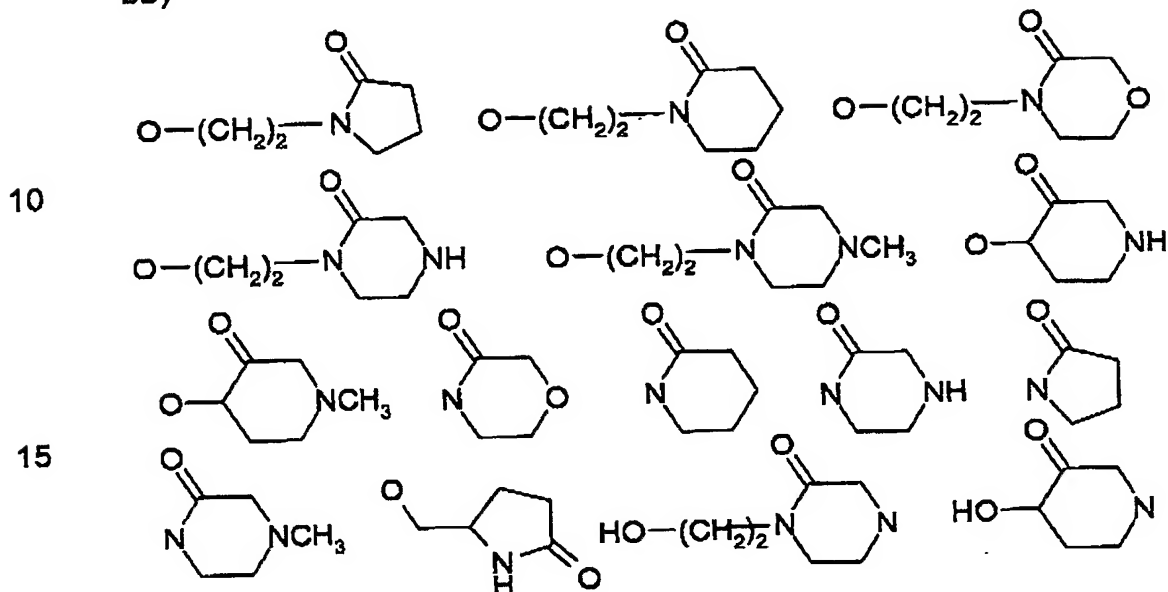
61



and/or bb):

5

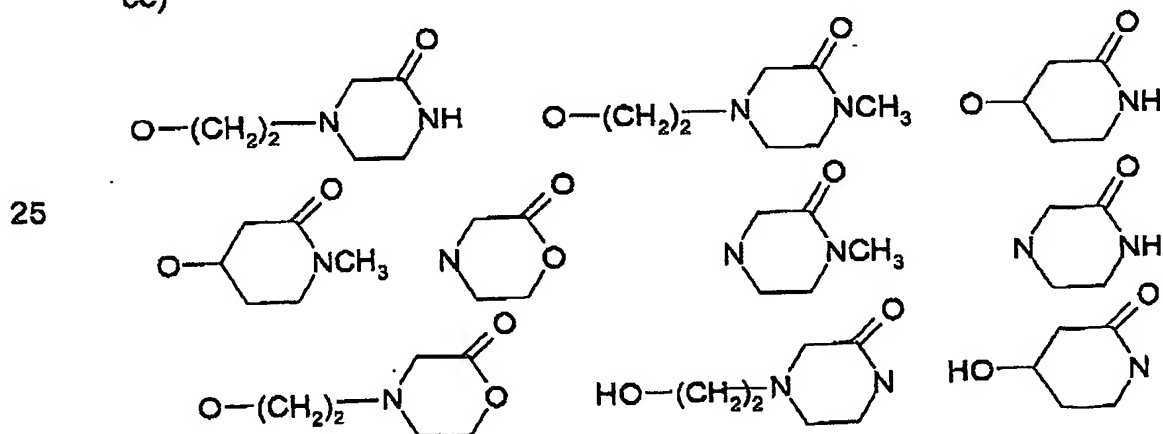
bb)



and/or cc):

20

cc)



30

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to

I.15), wherein Ar^1 comprises one or two, preferably one substituent R^8 that is selected from the group consisting of the formulae aa).

5 Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar^1 comprises two or more substituents R^8 , wherein one or two, preferably one substituent R^8 is selected from the group consisting of the formulae bb).

10 Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar^1 comprises two or more substituents R^8 , wherein one or two, preferably one substituent R^8 is selected from the group consisting of the formulae cc).

15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein Ar^1 comprises two or more substituents R^8 , wherein one or two, preferably one substituent R^8 is selected from the group consisting of SO_2CH_3 , SO_2CF_3 ,
20 OSO_2CH_3 , OSO_2CF_3 , SO_2NH_2 , $\text{SO}_2\text{NHCH}(\text{CH}_3)_2$, $\text{SO}_2\text{N}(\text{CH}_3)_2$, $\text{SO}_2\text{N}(\text{CH}_2\text{CH}_3)_2$ and 4-Morpholine-4-sulfonyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein
25 R^{10} is selected from A, CHAl_3 , $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} , $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$,
30 $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{COR}^{13}$ and $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, and more preferably from $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} , $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$,

$(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$ and $(CH_2)_nNR^{11}COOR^{13}$. In this embodiment, n is preferably 0 or 1 and/or k is preferably 1 or 2.

5

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein R^{10} is selected from A, $CHal_3$, NH_2 , $NR^{11}R^{12}$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kHet$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nCOR^{13}$ and $(CH_2)_nNR^{11}COOR^{13}$. and more preferably from A, $CHal_3$, NH_2 , $NR^{11}R^{12}$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and $(CH_2)_nNR^{11}COOR^{13}$ and especially from $NR^{11}R^{12}$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $COOR^{13}$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, COR^{13} , $CONR^{11}R^{12}$ and $NR^{11}COOR^{13}$. In this embodiment, n is preferably 0 or 1 and/or k is preferably 1 or 2. In this embodiment, R^{11} , R^{12} and/or R^{13} are preferably selected from H and A. In this embodiment, A is preferably selected from alkyl and especially from C_1 - C_4 -alkyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein in R^{10} , $COOR^{13}$ is preferably $COOA$, $NR^{11}COR^{13}$ is preferably $NHCOA$, $NR^{11}COOR^{13}$ is preferably $NHCOOA$ and/or $CONR^{11}R^{12}$ is preferably $CONHA$.

30 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein R^{10} is $COOR^{13}$, preferably $COOA$, $NR^{11}COR^{13}$, preferably $NHCOA$,

103224 do.doc

64

$\text{NR}^{11}\text{COOR}^{13}$, preferably NHCOOA and/or $\text{CONR}^{11}\text{R}^{12}$, preferably CONHA , and especially $\text{NR}^{11}\text{COR}^{13}$, preferably NHCOA , $\text{NR}^{11}\text{COOR}^{13}$, preferably NHCOOA and/or $\text{CONR}^{11}\text{R}^{12}$, preferably CONHA .

5 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein in R^{10} , A is preferably selected from substituted or unsubstituted alkyl, more preferred from substituted or unsubstituted $\text{C}_1\text{-C}_4$ -alkyl and even more preferred from unsubstituted $\text{C}_1\text{-C}_4$ -alkyl, and especially is methyl.

10

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein q is 1 or 2, i.e. the 6-membered carbocyclic substructure of the benzimidazolyl moiety is substituted by one or two substituents R^9 as defined above,

15

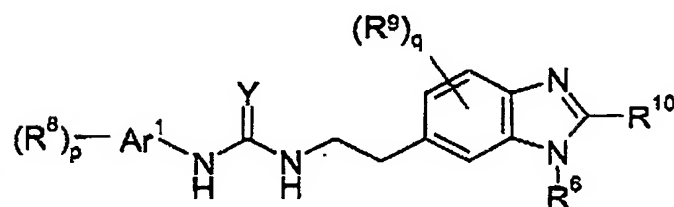
preferably one or two substituents selected independently from one another from alkyl and hal, and more preferably selected from CH_3 , CH_2CH_3 and hal.

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15), wherein one or more features of the above and below mentioned embodiments are combined in one compound.

20

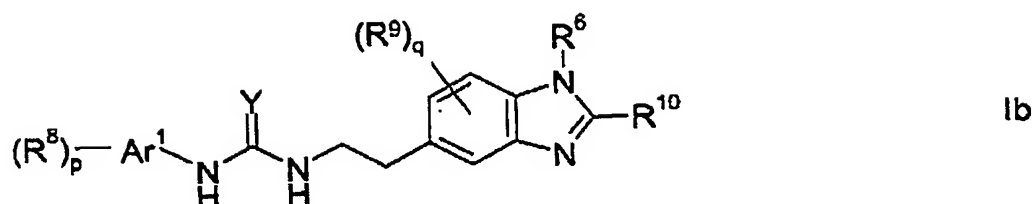
Subject of the present invention are therefore preferably compounds of formula I according to one or both of the formulae Ia and Ib,

25



Ia

30



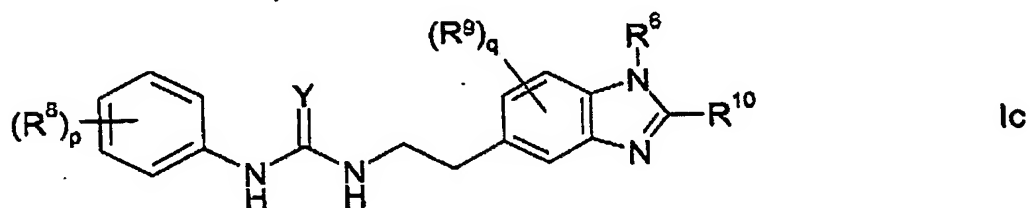
5

and the tautomeric forms thereof; wherein Ar^1 , R^8 , p , g , Y , R^9 , q , R^6 and R^{10} are as defined above and below, and preferably as defined in sub formulae I.1) to I.15) and/or the embodiments related thereto, and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

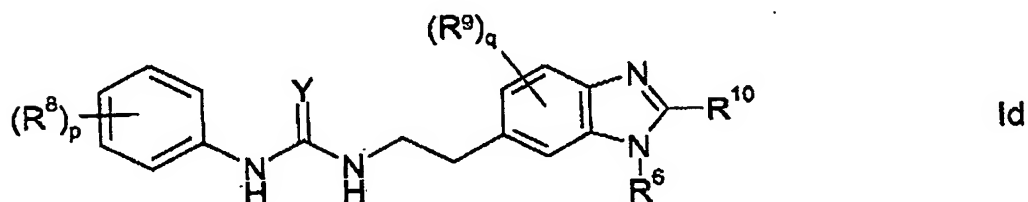
10

Subject of the present invention are therefore especially preferred compounds of formula I according to one or both of the formulae 1c and 1d,

15



20



25

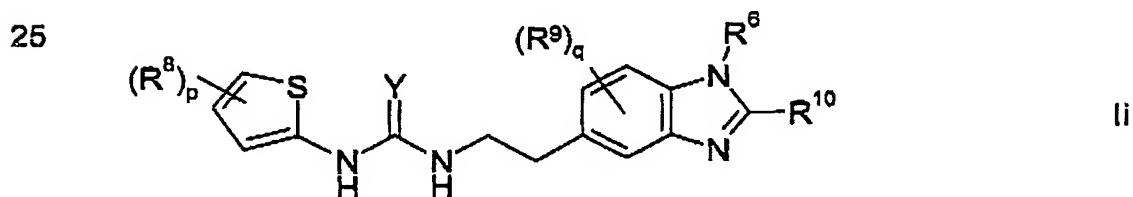
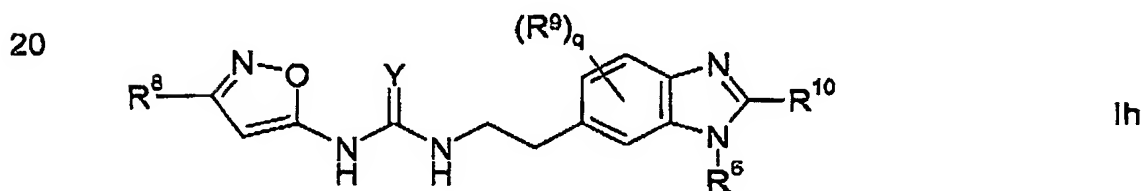
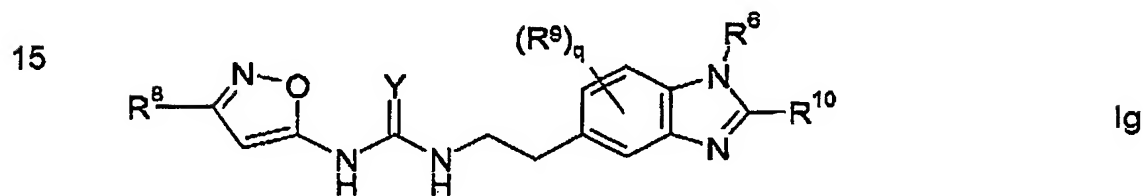
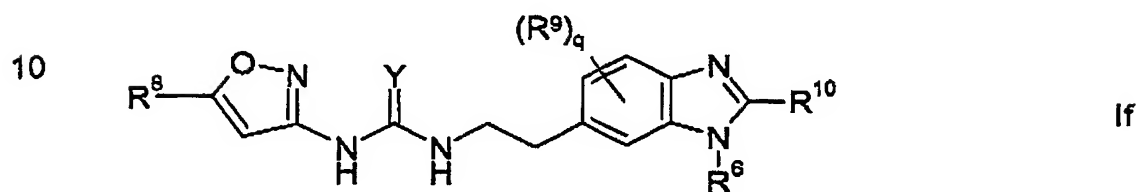
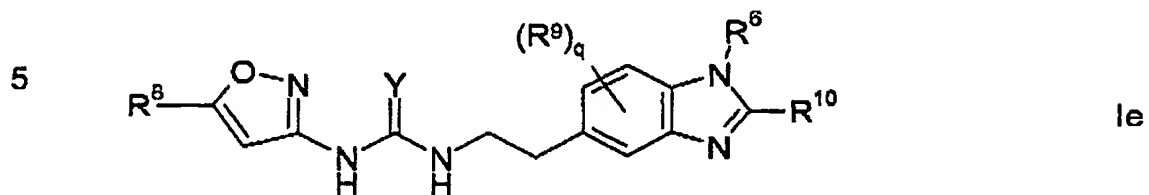
wherein Ar^1 , R^8 , p , Y , X , R^9 and q are as defined above and below, R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.15) and/or the embodiments related thereto;

30

103224 do.doc

66

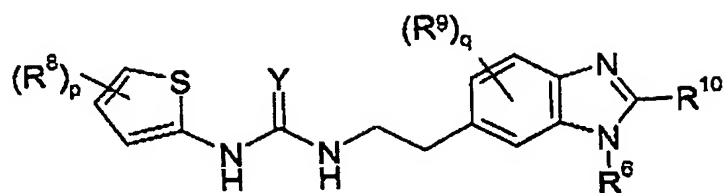
and/or compounds of formula I according to one or more of the formulae Ie to Ii,



30

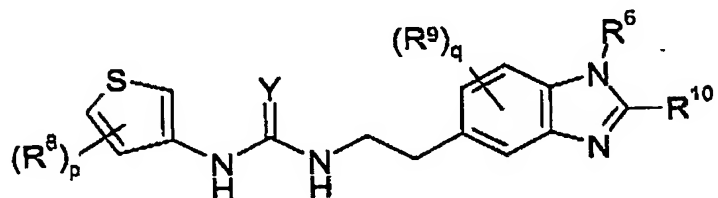
103224 do.doc

67



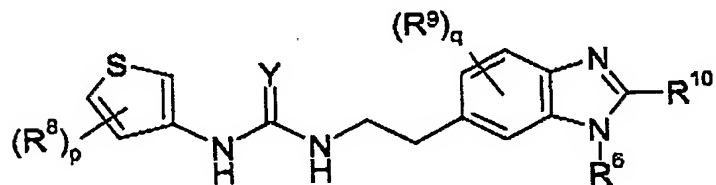
lj

5



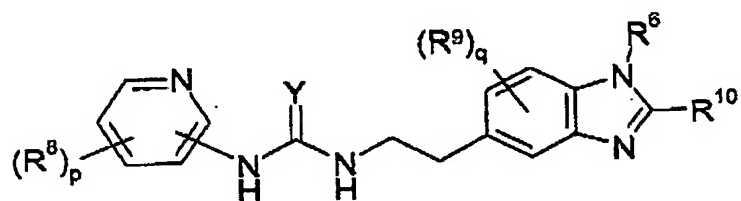
lk

10



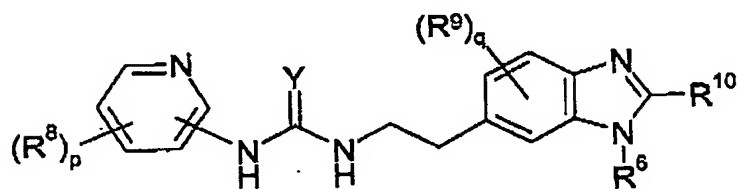
ll

15



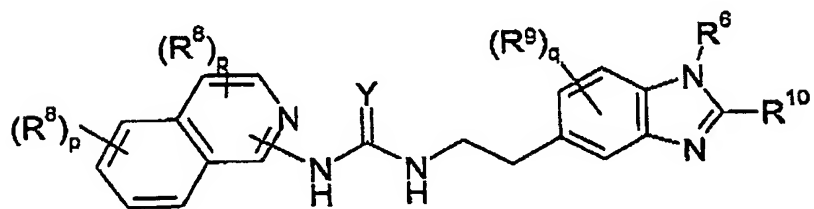
lm

20



ln

25

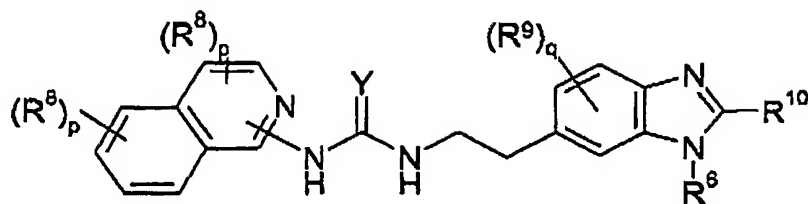


lo

30

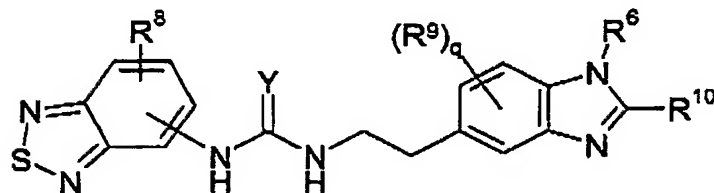
103224 do.doc

68



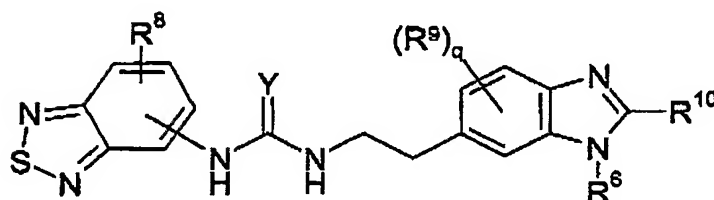
Ip

5



Iq

10



Ir

15

wherein R^8 , p , Y , R^9 and q are as defined above and below, R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.15) and/or the embodiments related thereto, the tautomeric forms thereof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

20

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.15) and Ia to Ir, wherein R^{10} is a substituted carbamoyl moiety CONHR^{23} or $\text{CONR}^{23}\text{R}^{24}$, preferably CONHR^{23} , wherein R^{23} and R^{24} are independently selected from the definitions given for R^8 , more preferably selected from $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{OR}^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of

30

$\text{CH}_2\text{CH}_2\text{NH}_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{OCH}_3$ and $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$.

Another preferred embodiment of the instant invention relates to compounds
 5 of formula I and preferably one or more of sub formulae I.1) to I.15) and Ia to
 Ir, wherein R^{10} is a substituted carbamoyl moiety CONHCH_3 .

Another preferred embodiment of the instant invention relates to compounds
 of formula I and preferably one or more of sub formulae I.1) to I.15) and Ia to
 10 Ir, wherein one or more of the substituents R^9 is a C_1 - C_4 alkyl residue,
 preferably an unsubstituted C_1 - C_4 alkyl residue, more preferably an
 unsubstituted alkyl residue selected from methyl, ethyl, n-propyl, isopropyl, n-
 butyl, sek.-butyl and tert.-butyl, more preferably selected from methyl and
 ethyl, and wherein q is 1, 2, or 3, more preferably 1 or 2.

15 Another preferred embodiment of the instant invention relates to compounds
 of formula I and preferably one or more of sub formulae I.1) to I.15) and Ia to
 Ir, wherein one or more of the substituents R^9 is selected from hal, preferably
 from F, Cl, Br and I and more preferably from F, Cl and Br.

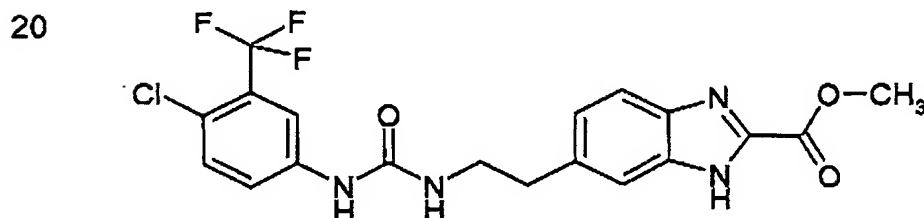
20 It is understood that when a residue, for example R^8 , R^9 , R^{10} or R^{14} or R^{23} , is
 comprised twice or more times in one or more of the formulae I and the sub
 formulae corresponding thereto, it is in each case independently from one
 another selected from the meanings given for the respective residue. For
 25 example, R^{11} and R^{12} are defined to be independently selected from a group
 consisting of H, A, $(\text{CH}_2)_m\text{Ar}^3$ and $(\text{CH}_2)_m\text{Het}$. Then
 $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_m\text{NR}^{12}\text{R}^{12}$ can be $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NA}_2$ (if $\text{R}^{11} = \text{A}$, $\text{R}^{12} = \text{A}$
 and $\text{R}^{12} = \text{H}$) as well as $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NHA}$ (if $\text{R}^{11} = \text{A}$, $\text{R}^{12} = \text{H}$ and $\text{R}^{12} = \text{A}$
 or $(\text{CH}_2)_n\text{NA}(\text{CH}_2)_m\text{NH}(\text{CH}_2)_m\text{Het}$ (if $\text{R}^{11} = \text{A}$, $\text{R}^{12} = \text{H}$ and $\text{R}^{12} = (\text{CH}_2)_m\text{Het}$).
 30 Accordingly, if a compound of formula I comprises one residue R^8 , R^9 and
 R^{10} , then for example R^8 , R^9 and R^{10} can all be $(\text{CH}_2)_n\text{COOR}^{13}$, wherein all
 residues R^{13} are the same (for example CH_2Hal , wherein Hal is Cl; then all

residues R^8 , R^9 and R^{10} are the same) or different (for example CH_2Hal , wherein in R^8 Hal is Cl; in R^9 Hal is F; and in R^{10} Hal is Br; then all residues R^8 , R^9 and R^{10} are different); or for example R^8 is $(CH_2)_nCOOR^{13}$, R^9 is NO_2 and R^{10} is $(CH_2)_nSR^{11}$, wherein R^{11} and R^{13} can be the same (for example both can be H or both can be A which is methyl) of different (for example R^{11} can be H and R^{13} can be A which is methyl).

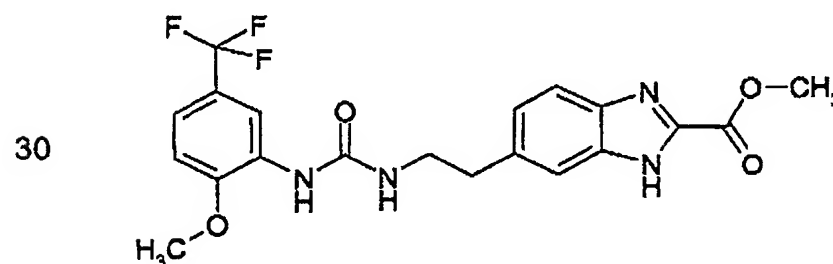
If not stated otherwise, reference to compounds of formula I and formula I also includes the sub formulae related thereto, especially sub formulae I.1) to I.15) and Ia to Ir.

Subject of the instant invention are especially those compounds of formula I and/or formula I, in which at least one of the residues mentioned in said formulae has one of the preferred or especially preferred meanings given above and below.

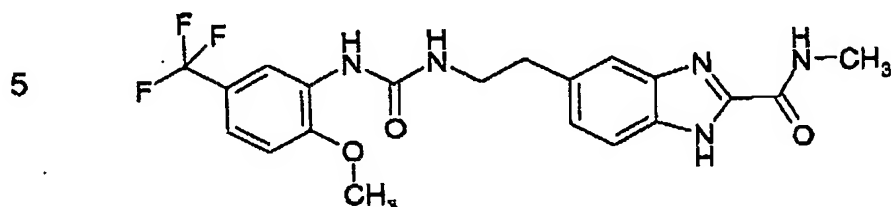
Especially preferred as compounds according to the invention are the compounds given below:



25 6-(2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-ethyl)-1H-benzimidazole-2-carboxylic acid methylester (MW = 440.81; Rt = 2.37)

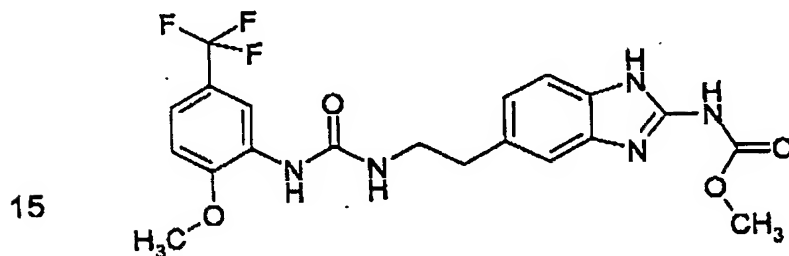


6-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazole-2-carboxylic acid methylester (MW = 436.39 Rt = 2.29)



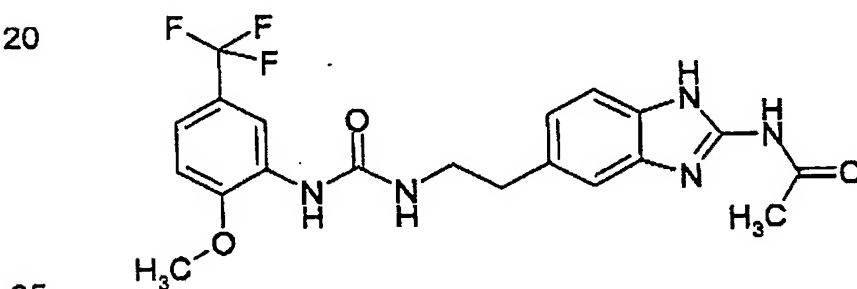
5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazole-2-carboxylic acid methylamide (MW = 435.40; Rt = 2.29)

10



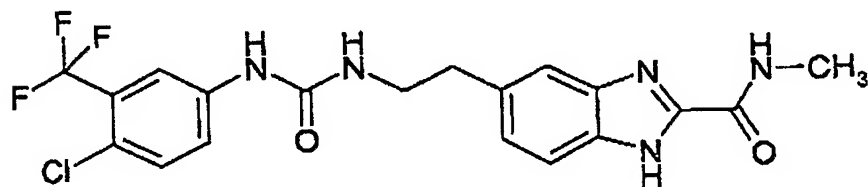
(5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazol-2-yl)-carbamic acid methyl ester (MW = 451.40; Rt = 2.06);

20



N-(5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazol-2-yl)-acetamide (MW = 435.40; Rt = 1.94);

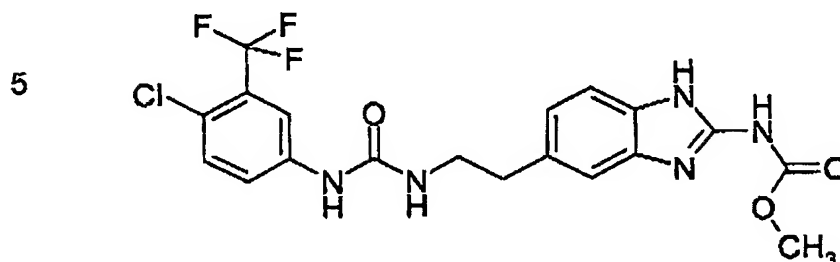
30



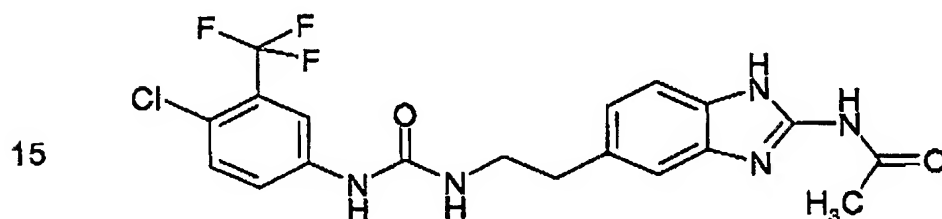
103224 do.doc

72

5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazole-2-carboxylic acid methylamide (MW = 439.82; Rt = 2.37);



10 (5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester (MW = 455.82; Rt = 2.11);



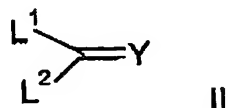
N-(5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide (MW = 439.8240; Rt = 2.05);

20 the tautomeric forms thereof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

25 The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

30 Another aspect of the invention relates to a method for producing compounds of formula I, characterised in that

a) a compound of formula II,



wherein

L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

is reacted with

b) a compound of formula III

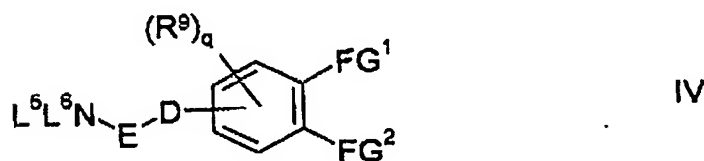


wherein

L^3 and L^4 are independently from one another H or a metal ion, and wherein R^6 and p are as defined above and below,

and

c) a compound of formula IV,



wherein

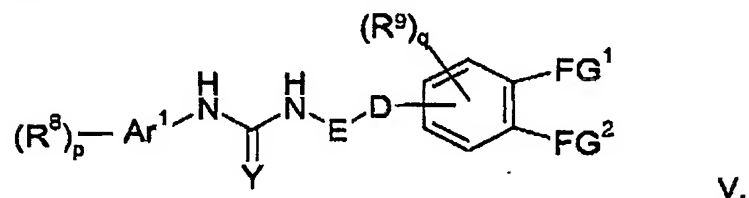
L^5 and L^6 are independently from one another H or a metal ion,

103224 do.doc

74

FG^1 is NHR^6 ,
 FG^2 is NH_2 oder NO_2 ,
 and E , D , R^9 , and q are as defined above and below, to
 obtain a compound of formula V

5

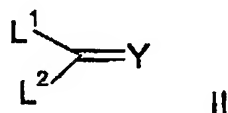


- 10 d) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 ,
 to transfer the NO_2 group into a NH_2 group,
 and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2
 is NH_2 , with $HalCN$ to obtain a compound of formula I, wherein R^{10} is
 NH_2 ;
 15 e) and optionally transferring the compound obtained from step d) into a
 compound of formula I, wherein R^{10} is other than NH_2 ,
 f) and optionally isolating and/or treating the compound of formula I as
 obtained by said reaction, with an acid, to obtain the salt thereof.

20 Another aspect of the invention relates to a method for producing compounds
 of formula I, characterised in that

- a) a compound of formula II,

25



wherein

30

L^1 and L^2 either independently from one another represent a leaving
 group, or together represent a leaving group, and Y is as
 defined above/below,

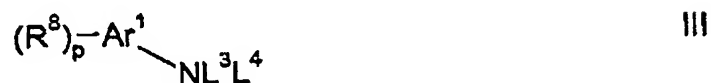
103224 do.doc

75

is reacted with

b) a compound of formula III

5



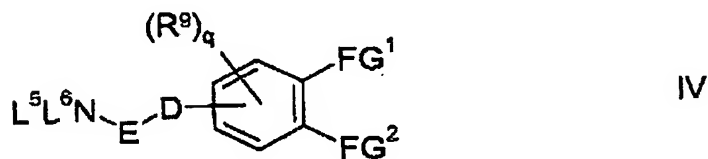
wherein

10

L^3 and L^4 are independently from one another H or a metal ion, and
wherein R^8 and p are as defined above and below,

and

15 c) a compound of formula IV,



20

wherein

L^5 and L^6 are independently from one another H or a metal ion,

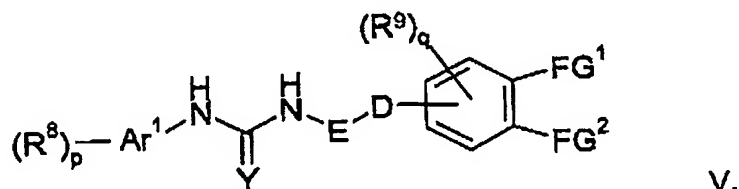
FG^1 is NHR^6 ,

25

FG^2 is NH_2 oder NO_2 ,

and E , D , R^9 , and q are as defined above and below, to obtain a
compound of formula V

30



103224 do.doc

76

- d) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 , to transfer the NO_2 group into a NH_2 group, and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2 is NH_2 , with $Hal_3C-C(=NH)OA$ to obtain a compound of formula I, wherein R^{10} is $CHal_3$;
- e) and optionally transferring the compound obtained from step d) into a compound of formula I, wherein R^{10} is other than $CHal_3$;
- f) and optionally isolating and/or treating the compound of formula I as obtained by said reaction, with an acid, to obtain the salt thereof.

Another aspect of the invention relates to a method for producing compounds of formula I, characterised in that

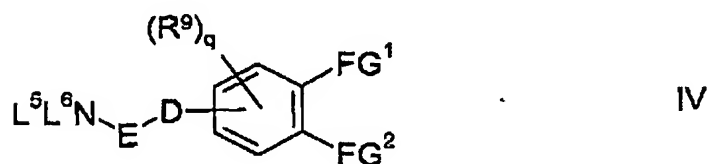
- a) a compound of formula IIIb



wherein

wherein R^8 , Ar^1 , p and Y are as defined above and below, is reacted with

- b) a compound of formula IV,

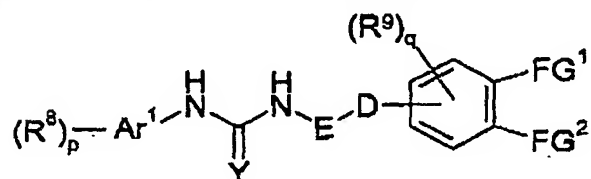


wherein

L^5 and L^6 are independently from one another H or a metal ion,
 FG^1 is NHR^6 ,

FG^2 is NH_2 oder NO_2 ,
and E, D, R^9 , and q are as defined above and below, to
obtain a compound of formula V

5

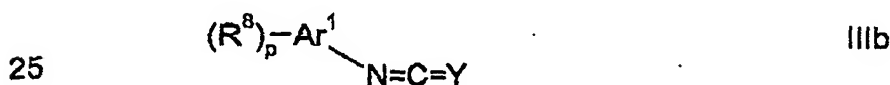


V,

- c) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 ,
to transfer the NO_2 group into a NH_2 group,
and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2
is NH_2 , with $HalCN$ to obtain a compound of formula I, wherein R^{10} is
 NH_2 ;
d) and optionally transferring the compound obtained from step c) into a
compound of formula I, wherein R^{10} is other than NH_2 ,
e) and optionally isolating and/or treating the compound of formula I as
obtained by said reaction, with an acid, to obtain the salt thereof.

Another aspect of the invention relates to an alternative method for producing
compounds of formula I, characterised in that

- a) a compound of formula IIIb



wherein

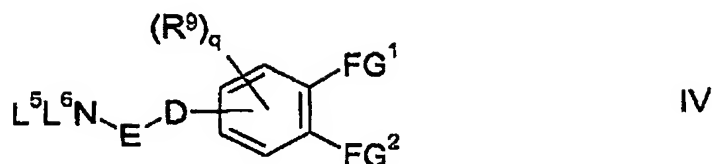
wherein R^8 , Ar^1 , p and Y are as defined above and below, is reacted
with

30

- b) a compound of formula IV,

103224 do.doc

78



5

wherein

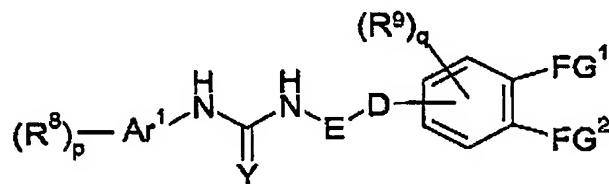
L^5 and L^6 are independently from one another H or a metal ion,

FG^1 is NHR^6 ,

FG^2 is NH_2 oder NO_2 ,

10

and E, D, R^9 , and q are as defined above and below, to obtain a compound of formula V



15

- c) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 , to transfer the NO_2 group into a NH_2 group, and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2 is NH_2 , with $Hal_3C-C(=NH)OA$ to obtain a compound of formula I, wherein R^{10} is $CHal_3$;
- d) and optionally transferring the compound obtained from step c) into a compound of formula I, wherein R^{10} is other than NH_2 ;
- e) and optionally isolating and/or treating the compound of formula I as obtained by said reaction, with an acid, to obtain the salt thereof.

20

25

The compounds of the formula I and also the starting materials for their preparation can be prepared by methods known per se, i. e. as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of

30

variants which are known per se, but are not mentioned here in greater detail.

5 If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I. On the other hand, it is possible to carry out the reaction stepwise.

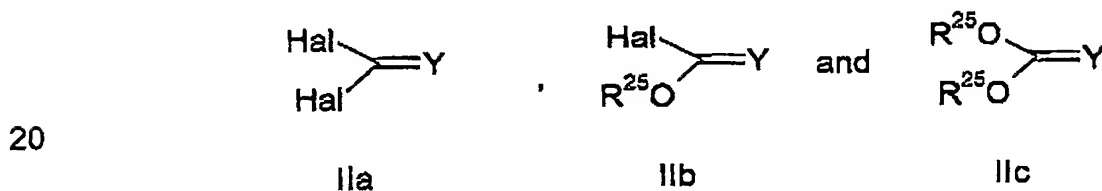
10 The compounds according to the invention can be manufactured or produced in an advantageous manner according to the methods of manufacture as described herein.

15 The reaction for the manufacture of compounds of formula I as described herein can be characterised as a carbonylation reaction of amines or the reaction of amines with carbon dioxide, carbon disulphide or derivatives or analogues thereof.

According to one aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 are preferably selected independently from one another from suitable leaving groups. Suitable leaving groups L^1 and L^2 for this type of reaction are known in the art, for example from the literature cited above. More preferably, L^1 and L^2 are independently selected from halogen, OR^{25} and $O-SO_2-R^{25}$. The residue R^{25} is preferably selected from substituted or unsubstituted alkyl groups and substituted or unsubstituted aryl groups, preferably substituted alkyl groups and substituted aryl groups. Preferred as alkyl groups in this respect are C_1 - C_4 -alkyl groups. Preferred as aryl group in this respect is phenyl. Suitable substituents for substituted alkyl groups are preferably selected from electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted alkyl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. Suitable substituents for substituted aryl groups are preferably selected from alkyl

- groups, preferably $C_1 - C_4$ alkyl groups, and electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted aryl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. If R^{25} is an unsubstituted alkyl group, it is preferably methyl. If R^{25} is a substituted alkyl group, it is preferably CF_3 or CCl_3 . If R^{25} is an unsubstituted aryl group, it is preferably phenyl. If R^{25} is a substituted aryl group, it is preferably selected from para-tolyl- (i. e. $p\text{-Me-C}_6\text{H}_4$) and para-Nitro-phenyl (i.e the $p\text{-O}_2\text{N-C}_6\text{H}_4$).
- Even more preferably, the leaving groups OR^{25} are selected from the para-Tosyl- (i. e. $p\text{-Me-C}_6\text{H}_4\text{-SO}_3$ -) group, the para-Nitro-phenolate- (i.e the $p\text{-O}_2\text{N-C}_6\text{H}_4\text{-O-}$) group and the triflate- (i. e. the $F_3\text{C-SO}_3$ -) group.

- Preferably, compounds of formula II, wherein L^1 and L^2 are selected independently from one another from suitable leaving groups, are selected from compounds IIa, IIb and IIc,



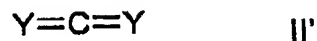
wherein Y, Hal and OR^{25} are as described above/below.

- According to another aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 together represent a leaving group. In this aspect, L^1 and L^2 together preferably represent Y as the leaving group, wherein the leaving group Y is as defined above/below and more preferably is O or S.

- According to this aspect of the method according to the invention, the compound of formula II is a compound of formula II',

103224 do.doc

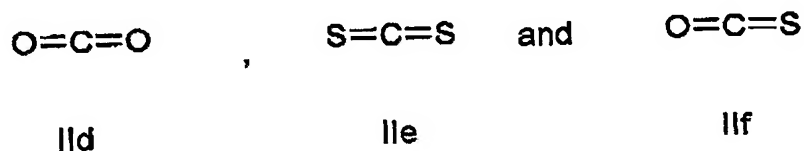
81



5 wherein each Y is independently selected from the meaning given above/below, and especially is independently selected from O and S.

According to this aspect of the method according to the invention, the compound of formula II is preferably selected from compounds of formula II'd, formula II'e and formula II'f,

10



15 more preferably of compounds of formula II'd and formula II'e. In this aspect, compounds of formula II'a are especially preferred.

In compounds of formula II, Y is preferably selected from O and S, and more preferably is O.

20

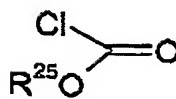
If compounds of formula II are desired wherein Y is other than O, it can be advantageous however to carry out the reaction according to the invention selecting a compound of formula II wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a C=NR²¹, C=C(R²²)-NO₂, C=C(R²²)-CN or C=C(CN)₂ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

25

30 In the method of manufacture according to the invention, the compound of formula II is even more preferably a compound of formula II'g,

103224 do.doc

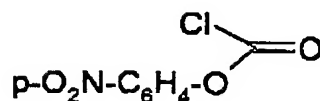
82



IIg

5

wherein R^{25} is as defined above/below, and especially a compound of formula IIh,



IIh.

10

In the compounds of formula III, L^3 and/or L^4 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na and K are especially preferred.

15

In the compounds of formula IV, L^5 and/or L^6 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na and K are especially preferred.

20

In case of multi-valent metal ions, the metal ions and the compounds of formula III and IV, respectively, form a complex containing one or more compounds of formula III and one or more metal ions wherein the ratio between the respective compounds and metal ions is depending on the valency of the metal ion(s) according to the rules of stoichiometry and/or electroneutrality.

30

103224 do.doc

83

In detail, the reaction of the compounds of formula II, formula III and formula IV is carried out in the presence or absence of a preferably inert solvent at temperatures between about -20°C and about 200°C , preferably between -10°C and 150°C and especially between 0°C or room temperature (25°) and 120° . In many cases, it is advantageous to combine one compound of formula III with one compound of formula IV at the lower end of the given temperature range, preferably between -20°C and 75°C , more preferred between 0°C and 60°C and especially between 10°C and 40°C , for example at about room temperature, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably between 65°C and 180°C , more preferred between 75°C and 150°C and especially between 80°C and 120°C , for example at about 80°C , at about 90°C or at about 100°C . Proceeding in that manner can be advantageous in the case that pound of formula II is the compounds of formula II'. If the compound of formula II is not a compound of formula II', the reaction can be regularly carried out without prolonged heating to higher temperatures. For example, it can preferably be carried out at a temperature between -10°C and 60°C , more preferably between -5°C and 40°C and even more preferably at about 0°C or at about room temperature (about 25°C). This given temperature range is especially advantageous, if the compound of formula II is selected from compounds of formula IIa, IIb, IIc and especially is a compound of formula IIg or IIh.

The method for manufacture according to the invention is preferably carried out in the presence of an acid binding means, for example one or more bases. This is especially advantageous, if the compound of formula II is selected from compounds of formula IIa – IIc an even preferred if the compound is selected from the compounds of formula IIg or formula IIh.

Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-

I03224 do.doc

84

earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), diaza bicyclo undecen (DBU), dimethyl
5 aniline, pyridine or quinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. Especially preferred as organic bases are pyridine and DIPEA. In many cases it is advantageous to employ two different organic bases and especially to use pyridine and
10 DIPEA.

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily
15 determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 36 hrs, preferably 30 min and 24 hrs and especially between 45 min and 18 hrs, for example about 1 h, about 2 hrs, about 4 hrs, about 6 or about 18 hrs.

20 Preferably, the reaction of the compounds of the formula II, III and IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; 25 chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or 30 ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as

103224 do.doc

85

acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are chlorinated hydrocarbons, especially dichloromethane, and amides, especially DMF. Especially preferred is dichloromethane.

In compounds of formula IIIb, $-N=C=Y$ is preferably $-N=C=O$ or $-N=C=S$ and especially preferably $-N=C=O$.

If compounds of formula II are desired wherein Y is other than O, it can be advantageous however to carry out the reaction of a compound of formula IIIb, wherein Y is O, and a compound of formula IV according to the invention to obtain a compound of formula I, wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a $C=NR^{21}$, $C=C(R^{22})-NO_2$, $C=C(R^{22})-CN$ or $C=C(CN)_2$ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

In detail, the reaction of the compounds of the formula IIIb with the compounds of the formula IV is carried out in the presence or absence of a preferably inert solvent at temperatures between about $-20\text{ }^{\circ}\text{C}$ and about $200\text{ }^{\circ}\text{C}$, preferably between $-10\text{ }^{\circ}\text{C}$ and $150\text{ }^{\circ}\text{C}$ and especially between $0\text{ }^{\circ}\text{C}$ or room temperature (25°) and 120° . If $-N=C=Y$ is selected from $-N=C=O$ or $-N=C=S$ and especially is $-N=C=O$, the reaction can be regularly carried out without prolonged heating to higher temperatures. For example, it can preferably be carried out at a temperature between $-10\text{ }^{\circ}\text{C}$ and $60\text{ }^{\circ}\text{C}$, more preferably between $-5\text{ }^{\circ}\text{C}$ and $40\text{ }^{\circ}\text{C}$ and even more preferably at about $0\text{ }^{\circ}\text{C}$ or at about room temperature (about 25°C).

I03224 do.doc

86

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring.

- 5 Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 36 hrs, preferably 30 min and 24 hrs and especially between 45 min and 16 hrs, for example about 1 h, about 2 hrs, about 4 hrs, about 6 or about 16 hrs.
- 10 Preferably, the reaction of the compounds of the formula IIIb with the compounds of the formula IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as
- 15 trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether
- 20 (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.
- 25 Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are chlorinated hydrocarbons, especially dichloromethane, and sulfoxides, especially DMSO. Especially preferred is dichloromethane.

30

Preferably, the reaction between a compound of formula IIIb wherein

103224 do.doc

87

5 $-N=C=Y$ is $-N=C=O$ or $-N=C=S$ and especially is $-N=C=O$, and a compound of formula IV, especially a compound of formula IV, wherein L^1 , L^2 and L^3 is H, is carried out in an inert solvent at the lower end of the given temperature range, for example in a chlorinated hydrocarbon, for example dichloromethane, in a temperature range between -10°C and 60°C , preferably at about 0°C or at about room temperature (about 25°C). Reaction times generally lie in the range of 30 min hours to 24 hrs, preferably 1h to 6 hrs, for example at about 1h, at about 2 hrs, at about 3 hrs or about 5 hrs. Preferably, no acid binding means is present.

10 The reducing step starting from a compound of formula V, wherein FG^2 is NO_2 , to a compound of formula V, wherein FG^2 is NH_2 , can be performed according to methods known in the art. In an advantageous manner, it can be performed by a hydrogenating reaction. Methods and reaction conditions for
15 hydrogenating a NO_2 -moiety into a NH_2 -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, for example Pd/C or Raney-nickel, preferably Raney-nickel. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable
20 solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. Preferred as solvent is a mixture of THF/methanol, preferably in about equal measures. In general, the
25 hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150° , preferably 0° and 50° , such as about room temperature.

30 In compounds of formula $Hal_3C-C(=NH)OA$, Hal is preferably as defined above/below, more preferably Cl, Br and/or I and especially is Cl.

103224 do.doc

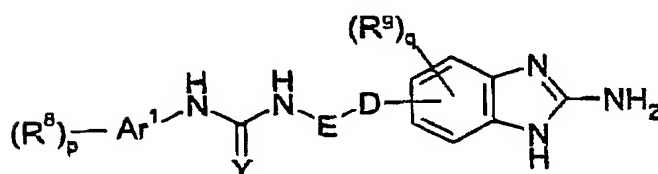
88

In compounds of formula HalCN, Hal is preferably as defined above/below and more preferably Br.

5 Compounds of formula I, wherein R^{10} is $CHal_3$ or NH_2 , can be readily transformed into compounds of formula I, wherein R^{10} is other than $CHal_3$ or NH_2 , by a variety of methods known in the art, for example from Houben-Weyl, Methoden der organischen Chemie. Suitable methods include, but are not limited to solvolysing methods, such as hydrolysing methods, aminolysing methods and partial or a total saponification, optionally followed
10 by further transformation steps, such as partial or full reduction reactions, oxidation reactions, acylation reactions, alkylation reactions, arylation reaction, addition reactions and/or substitution reactions.

For example, compounds of formula V, wherein R^{10} is NH_2 can be transferred
15 into amino derivatives, for example amides, imides, carbamates, ureas and thio ureas, for example by acylation reactions and/or addition reactions, with compounds such as carbonic acids and carbonic acids derivatives, for example acid chlorides, esters, isocyanides, thio isocyanides and chloroformates; into secondary, tertiary or quaternary amines, for example
20 by alkylation or arylation reactions. Various such reactions and reagents are known in the art, for example from Houben-Weyl, Methoden der organischen Chemie.

For example, a compound of formula V, wherein R^{10} is NH_2 ,
25

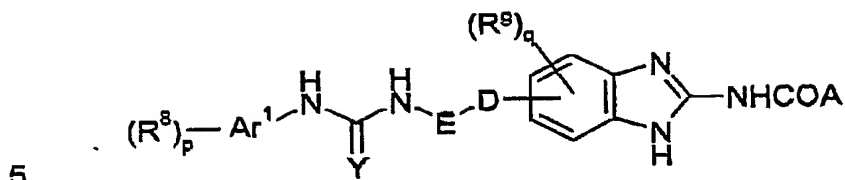


30

can be readily transformed into a compound of V, wherein R^{10} is $NHCOA$ ($= NH-(CO)-A$),

103224 do.doc

89

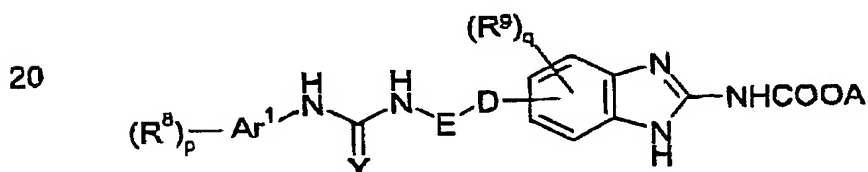


for example by reaction with and acid halide HalCOA (= Hal-(CO)-A, wherein the residue A is independently selected from the meanings given for A above/below in the absence or preferably in the presence of an acid binding means, such as pyridine or DIPEA. The analogous reaction with HalCOR¹³ leads to compounds of formula I, wherein R¹⁰ is NHCOR¹³ and R¹³ is as defined above/below.

10

Acylation of a compound of formula V, wherein R¹⁰ is NH₂, with a chloroformate, such as HalCOOA (= Hal-(CO)-OA), in the absence or preferably presence of an acid binding means, such as pyridine or DIPEA, leads to the respective carbamate,

15



wherein each residue A is independently selected from the meanings given for A above/below. The analogous reaction with HalCOOR¹³ leads to compounds of formula I, wherein R¹⁰ is NHCOOR¹³ and wherein R¹³ is as defined above/below.

25

In compounds of formula HalCOA, HalCOR¹³, HalCOOA and HalCOOR¹³, Hal is preferably as defined above/below, more preferably Cl, Br and/or I and especially is Cl.

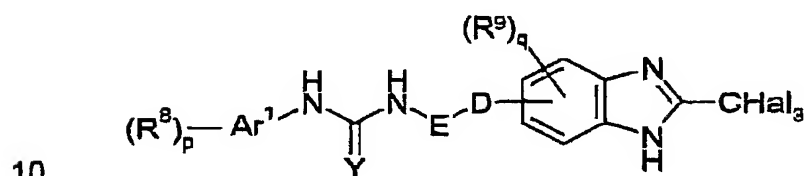
30

103224 do.doc

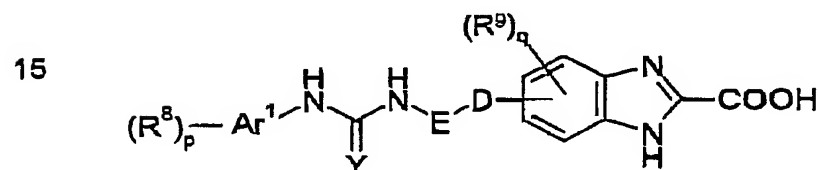
90

For example, compounds of formula V, wherein R^{10} is $CHal_3$ can be transferred into carbonic acids and carbonic acids derivatives, for example under solvolysing or hydrolysing conditions.

5 For example, a compound of formula V, wherein R^{10} is $CHal_3$,

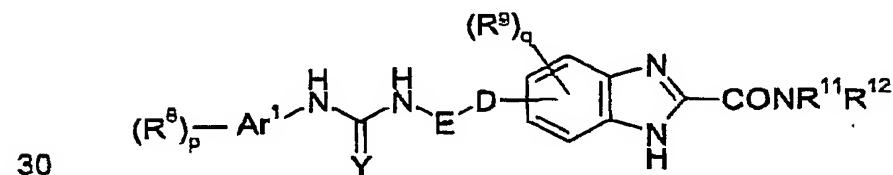


can be readily transformed into a compound of V, wherein R^{10} is $COOH$,



for example under hydrolysing conditions, such as in water or a watery solvent, such as a mixture of water and alcohol, for example methanol or ethanol, in the presence of a base, for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate, which subsequently can be transformed into any carbonic acids derivatives, such as imines, esters and amides. For example, reacting the carbonic acid with $HNR^{11}R^{12}$ leads to compounds of formula I, wherein R^{10} is $CONR^{11}R^{12}$.

25



**Fax**

An Europäisches Patentamt
 80298 München

Von Merck Patent GmbH
 Patents Pharmaceuticals
 Dr. Dotzauer

E-Mail patent@merck.de

Telefon +49 (0) 6151 72-4371

Fax +49 (0) 6151 72-7191

Datum 26.02.2004

Fax +49 89 2399 4465
Seiten 55

Antrag auf Erteilung eines europäischen Patents vom 26.02.2004
Zeichen des Anmelders: 103224-do/ki
Titel: „Benzimidazolyl derivatives“

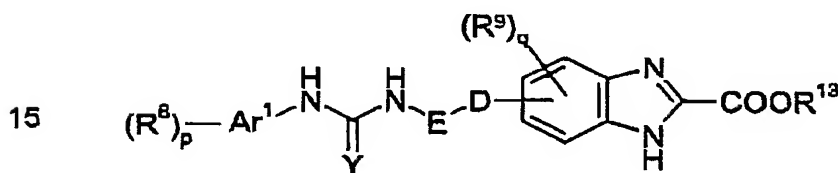
Teil 3: Fax (1 Seite)
Anmeldung (Seite 91-144)

103224 do.doc

91

wherein each residue R^{11} and R^{12} is independently selected from the meanings given for above/below. Preferably, R^{11} and R^{12} are independently selected from H and A. More preferably, R^{11} is H and R^{12} is A. The analogous reaction with HNA_2 leads to compounds of formula I, wherein R^{10} is $CONA_2$, wherein each residue A is independently selected from the meanings given for A above/below. Subsequent reduction of the respective CO group readily leads to the corresponding respective amines.

For example, a compound of formula I, wherein R^{10} is $COOH$, can be reacted with HOR^{13} , for example under dehydrating conditions, to give compounds of formula I,



wherein R^{10} is $COOR^{13}$, wherein R^{13} is selected from the meanings given above/below. Preferably, R^{13} is A. The compound of formula I, wherein R^{10} is $COOR^{13}$ can alternatively be obtained by transferring a compound of formula I, wherein R^{10} is $COOH$, into a compound of formula I, wherein R^{10} wherein R^{10} is $COHal$ and reacting it with HOR^{13} . Subsequent reduction of the respective CO group readily leads to the corresponding respective ethers.

25 In general, the compounds of formula III, IIIb, IV and/or formula V are new. In any case, they can be prepared according to methods known in the art.

The compounds of formula IIIb can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by one or more of the reaction routes given below:

103224 do.doc

92

Compounds of formula IIIb, wherein Y is O or S can be readily obtained from suitable substituted derivatives of $(R^8)_p-Ar^1$ according to known procedures for producing isocyanates and thioisocyanates. When Y is O, the compounds of formula IIIb can be readily obtained via Curtius-, Hoffmann or Lossen rearrangement starting from $(R^8)_p-Ar^1-COOH$ or the respective acid halides, as described in the art. If desired, compounds of formula III, wherein Y is O can be readily derivatized to compounds of formula IIIb, wherein Y is S or NR^{21} , according to procedures known in the art.

The compounds of formula III can be advantageously produced starting from a compound of formula (A)



wherein, R^8 , p and Ar^1 are as defined above/below, and transferring it into a compound of formula (B);



according to methods known in the art. Advantageously, the compound of formula (A) then can be transferred into a compound of formula (B) by a nitration reaction. Suitable methods and reaction conditions for nitration reactions are known in the art. Advantageously, the compounds of formula (A) can be obtained by reacting a compound of formula (B) with nitrating acid or a combination of concentrated sulfuric acid and potassium nitrate. If a combination of concentrated sulfuric acid and potassium nitrate is used, it can be advantageous to perform the reaction at a relatively low temperature, for example between $-20\text{ }^{\circ}\text{C}$ and $+50\text{ }^{\circ}\text{C}$, preferably between $-10\text{ }^{\circ}\text{C}$ and room temperature, more preferred between $-5\text{ }^{\circ}\text{C}$ and $0\text{ }^{\circ}\text{C}$.

I03224 do.doc

93

The compound of formula (B) then can be transferred into the compound of formula III by methods known in the art.

5 The compound of formula (B) then can be transferred into a compound of formula III according to methods known in the art.

Advantageously, the compound of formula (B) can be transferred into a compound of formula III, wherein L^3 and L^4 are hydrogen, preferably by a reduction reaction or hydrogenating reaction, preferably a hydrogenating
10 reaction. Methods and reaction conditions for hydrogenating a NO_2 -moiety into a NH_2 -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, for example Pd/C or Raney-nickel, preferably Raney-nickel. In general, such hydrogenation reactions are carried out in a suitable
15 solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. Preferred as solvent is a mixture of THF/methanol, preferably in about equal measures. In general, the hydrogenation reactions are carried out at about normal pressure or slightly
20 elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150° , preferably 0° and 50° . The obtained compound of formula III wherein L^3 and L^4 are hydrogen can optionally be isolated and/or purified and then optionally transferred into a
25 compound of formula III wherein L^3 and L^4 are other than hydrogen, for example according to methods and reaction conditions as described herein.

30 The compounds of formula IV can be obtained according to methods known in the art, for example as described in Houben-Weyl, Methods of Organic Chemistry.

103224 do.doc

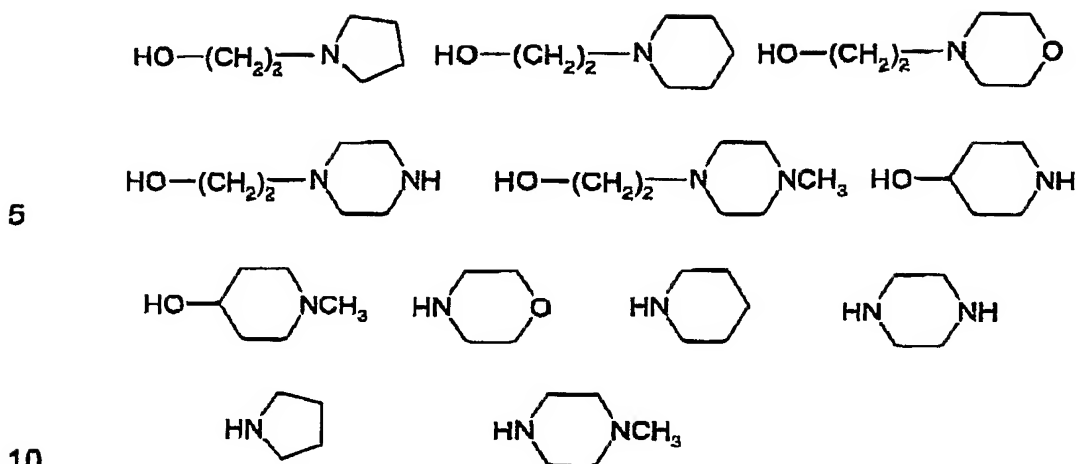
94

Independently of the chosen reaction route, it is in many cases possible or even feasible to introduce residues R^8 , R^9 and/or R^{10} into one or more of the compounds described above, or, if the compound already comprises one or more residues R^8 , R^9 and/or R^{10} , to introduce additional residues R^8 , R^9 and/or R^{10} into said compound. The introduction of additional residues can be readily performed by methods known in the art and especially by aromatic substitution, for example nucleophilic aromatic substitution or electrophilic aromatic substitution. For example, in compounds comprising Ar^1 , wherein Ar^1 comprises one or more halogen and preferably fluorine substituents, one or more of the halogen/fluorine substituents can be easily substituted by hydroxy, thio and/or amino substituted hydrocarbons, preferably selected from the group consisting of $HO(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_kR^{13}$, $HO(CH_2)_kOR^{11}$, $HO(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $HO(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_nCOOR^{13}$, $HO(CH_2)_nS(O)_uR^{13}$, $HNR^{11}(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_kOR^{11}$, $HNR^{11}(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_nCOOR^{12}$ and $HNR^{11}(CH_2)_nS(O)_uR^{13}$, and the metal salts thereof, wherein R^{11} , R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. Even more preferred, the hydroxy, thio and/or amino substituted hydrocarbons are selected from the group consisting of NH_3 , $HN(CH_3)_2$, NH_2CH_3 , $HN(C_2H_5)_2$, $H_2NCH_2CH_2NH_2$, $HOCH_2CH_2NH_2$, $HOCH_2CH_2NHCH_3$, $HN(CH_3)CH_2CH_2NH_2$, $HN(CH_3)CH_2CH_2N(CH_3)_2$, $HN(CH_3)CH_2CH_2N(CH_3)_2$, $HN(CH_3)CH_2CH_2OCH_3$, $HOCH_2CH_2N(CH_3)_2$, $HOCH_2CH_2N(CH_2CH_3)_2$, $HSCH_3$, HSC_2H_5 , and compounds of the formulae

30

I03224 do.doc

95



or salts and especially metal salts thereof.

15 On the other hand, it is in many cases possible or even feasible to modify or derivatize one or more of the residues R⁸, R⁹ and/or R¹⁰ into residues R⁸, R⁹ and/or R¹⁰ other than the ones originally present. For example, CH₃-groups can be oxidized into aldehyde groups or carbonic acid groups, thio atom containing groups, for example S-alkyl or S-aryl groups, can be oxidized into SO₂-alkyl or SO₂-aryl groups, respectively, carboxylic acid groups can be

20 derivatized to carboxylic acid ester groups or carboxylic acid amide groups and carboxylic acid ester groups or carboxylic acid amide groups can be hydrolysed into the corresponding carboxylic acid groups. Methods for performing such modifications or derivatizations are known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

25

Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic

30 Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures,

103224 do.doc

digesting procedures, filtration procedures, chromatography, chromatography by HPLC and drying procedures, especially drying procedures in vacuo and/or elevated temperature.

- 5 A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic
- 10 acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for
- 15 example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic
- 20 acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose
- 25 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into
- 30 the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the

103224 do.doc

97

dimethyl-, diethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

5

On the other hand, if desired, the free bases of the formula I can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

10

The invention relates to compounds of the formula I and physiologically acceptable salts and solvates thereof as medicaments.

The invention also relates to the compounds for the formula I and physiologically acceptable salts and solvates thereof as kinase inhibitors.

15

The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. In this cases, one or more compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

20

25

The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, solvates of compounds of the formula I, salts of compounds of formula I, for the production of pharmaceutical compositions and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more

30

103224 do.doc

compounds according to the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. In this respect, active ingredients are preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds according to invention which are disclosed herein.

The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation preferably according to invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients, auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

103224 do.doc

99

Preferably, one or more compounds according to the invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries, adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to methods known in the art, for example as described below:

- | | | |
|----|---------------------------------------|--|
| 15 | tablets | mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression |
| 20 | capsules | mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules |
| 25 | semi-solids (ointments, gels, creams) | dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty resp. aqueous phase, homogenisation (creams only) |
| 30 | suppositories (rectal and vaginal) | dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into |

103224 do.doc

101

The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind
5 of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for example by the doctor or physician which advises or attends the therapeutic treatment.

10

However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament
15 combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred. Oral administration is especially preferred.

20

These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as
25 lactose or starch, magnesium stearate, talc or vaseline. Examples for suitable dosage forms, which are especially suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops. Further examples for suitable dosage forms, which are especially suitable for rectal administration are suppositories, further
30 examples for suitable dosage forms, which are especially suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for

103224 do.doc

102

topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The compositions and/or preparations indicated may be sterilized and/or comprise assistants, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavors and/or one or more further active ingredients, for example one or more vitamins.

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO₂ or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

The compounds of the formula I and their physiologically acceptable salts and solvates can be employed for combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

In General, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination

103224 do.doc

103

and severity of the particular illness to which the therapy applies. Oral administration is preferred.

5 The compounds of the formula I according to claim 1 and/or their physiologically acceptable salts are also used in pathological processes which are maintained or propagated by angiogenesis, in particular in tumors, restenoses, diabetic retinopathy, macular degenerative disease or rheumatois arthritis.

10 Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred
15 means is to measure the physiological potency of a given compound.

For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according to the invention, particularly other anti-metastatic, antitumor or anti-angiogenic
20 agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc. Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-C, BICNU, busulfan, CNNU, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, hydrea, ifosfarnicle, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen
25 mustard, velban, vincristine, vinblastine, VP-16, carboplatinum, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

30 The compounds of the invention have been shown to have antiproliferative effect in an in vivo xenograft tumor model. The subject compounds are administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a lymphoproliferative

103224 do.doc

104

disorder, to inhibit graft rejection, or neurological damage due to tissue repair, etc. The present compounds are useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is preferably also used to refer to both prevention of disease, and treatment of pre-existing conditions. The prevention of proliferation is accomplished by administration of the subject compounds prior to development of overt disease, e.g., to prevent the regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc. Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

The host, or patient, may be from any mammalian species, e.g., primate sp., particularly human; rodents, including mice, rats and hamsters; rabbits; equines, bovines, canines, felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

The susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to induce cell death or inhibit migration, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used. The viable cells left after treatment are then counted.

The dose will vary depending on the specific compound utilized, specific disorder, patient status, etc. Typically a therapeutic dose will be sufficient to substantially decrease the undesirable cell population in the targeted tissue, while maintaining patient viability. Treatment will generally be continued until there is a substantial reduction, e.g., at least about 50 %, decrease in the cell burden, and may be continued until there are essentially none of the undesirable cells detected in the body.

103224 do.doc

105

The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

5

The compounds also find use in the specific inhibition of a signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling pathways, for example to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle regulation or in response to extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include psoriasis, arthritis, inflammation, endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins preferably raf kinases, e.g., there is a decrease in the phosphorylation of a specific substrate in the presence of the compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.

20

There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of a variety of conditions where there is proliferation and/or migration of smooth muscle cells, and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that vessel, e.g., neointimal occlusive lesions. Occlusive vascular conditions of interest include atherosclerosis, graft coronary vascular disease after transplantation, vein

30

103224 do.doc

106

graft stenosis, peri-anastomatic prothetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

5 Diseases where there is hyperproliferation and tissue remodelling or repair or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds. The growth and proliferation of neural cells is also of interest.

10 Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-modulate cell death (apoptosis) and activate angiogenesis to product a tumor neovasculature.

15 Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial, stomach, dysplastic oral mucosa, polyposis, invasive oral cancer, non-small cell lung carcinoma, transitional and squamous cell urinary carcinoma etc.;
20 neurological malignancies; e.g. neuroplastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis fungoides, non-MF cutaneous T-cell-lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid hyperplasia, bullous pemphigoid, discoid lupus
25 erythematosus, lichen planus, etc.; and the like.

Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas, etc. Some cancers of particular interest include breast cancers, which are primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most
30 common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized

I03224 da.doc

107

through the wall of the duct and invaded the fatty tissue of the breast.

Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has the potential to metastasize elsewhere in the body. About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

5

Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer. Epidermoid carcinoma (also called squamous cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

10

15

20

25

30

Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

103224 do.doc

108

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocytes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

Surprisingly, it has been found that benzimidazolyl derivatives according to invention are able to interact with signaling pathways, especially the signaling pathways described herein and preferably the raf-kinase signaling pathway. Benzimidazolyl derivatives according to the invention preferably show advantageous biological activity which can easily be demonstrated according to methods known in the art, for example by enzyme based assays. Suitable assays are known in the art, for example from the literature cited herein and the references cited in the literature, or can be developed and/or performed in an analogous manner thereof. In such enzyme based assays, benzimidazolyl derivatives according to invention show an effect, preferably a modulating and especially an inhibiting effect which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferred in the nanomolar range.

ID3224 do.doc

109

In general, compounds according to the invention are to be regarded as suitable kinase-modulators and especially suitable kinase-inhibitors according to the invention if they show an effect or an activity to one or more kinases, preferably to one or more raf-kinases that preferably lies,
5 determined as IC_{50} -value, in the range of 100 μ mol or below, preferably 10 μ mol or below, more preferably in the range of 3 μ mol or below, even more preferably in the range of 1 μ mol or below and most preferably in the nanomolar range. Especially preferred for use according to the invention are kinase-inhibitors as defined above/below, that show an activity, determined
10 as IC_{50} -value, to one or more raf-kinases, preferably including A-raf, B-raf and c-raf1 or consisting of A-raf, B-raf and c-raf1 and more preferred including c-raf1 or consisting of c-raf1, in the range of 0.5 μ mol or below and especially in the range of 0.1 μ mol or below. In many cases an IC_{50} -value at the lower end of the given ranges is advantageous and in some cases it is
15 highly desirable that the IC_{50} -value is as small as possible or the IC_{50} -values are as small as possible, but in general IC_{50} -values that lie between the above given upper limits and a lower limit in the range of 0.0001 μ mol, 0.001 μ mol, 0.01 μ mol or even above 0.1 μ mol are sufficient to indicate the desired pharmaceutical activity. However, the activities measured can vary
20 depending on the respective testing system or assay chosen.

Alternatively, the advantageous biological activity of the compounds according to the invention can easily be demonstrated in *in vitro* assays, such as *in vitro* proliferation assays or *in vitro* growth assays. Suitable *in vitro*
25 assays are known in the art, for example from the literature cited herein and the references cited in the literature or can be performed as described below, or can be developed and/or performed in an analogous manner thereof.

As an example for an *in vitro* growth assay, human tumor cell lines, for
30 example HCT116, DLD-1 or MiaPaCa, containing mutated K-ras genes can be used in standard proliferation assays, for example for anchorage dependent growth on plastic or anchorage independent growth in soft agar.

103224 do.doc

110

Human tumor cell lines are commercially available, for example from ATCC (Rockville MD), and can be cultured according to methods known in the art, for example in RPMI with 10% heat inactivated fetal bovine serum and 200 mM glutamine. Cell culture media, fetal bovine serum and additives are commercially available, for example from Invitrogen/Gibco/BRL (Karlsruhe, Germany) and/or QRH Biosciences (Lenexa, KS). In a standard proliferation assay for anchorage dependent growth, 3×10^3 cells can be seeded into 96-well tissue culture plates and allowed to attach, for example overnight at 37 °C in a 5% CO₂ incubator. Compounds can be titrated in media in dilution series and added to 96 well cell cultures. Cells are allowed to grow, for example for 1 to 5 days, typically with a feeding of fresh compound containing media at about half of the time of the growing period, for example on day 3, if the cells are allowed to grow 5 days. Proliferation can be monitored by methods known in the art, such as measuring metabolic activity, for example with standard XTT colorimetric assay (Boehringer Mannheim) measured by standard ELISA plate reader at OD 490/560, by measuring ³H-thymidine incorporation into DNA following an 8 h culture with 1 μCi ³H-thymidine, harvesting the cells onto glass fiber mats using a cell harvester and measuring ³H-thymidine incorporation by liquid scintillation counting, or by staining techniques, such as crystal violet staining. Other suitable cellular assay systems are known in the art.

Alternatively, for anchorage independent cell growth, cells can be plated at 1×10^3 to 3×10^3 in 0.4% Seaplaque agarose in RPMI complete media. overlaying a bottom layer containing only 0.64% agar in RPMI complete media, for example in 24-well tissue culture plates. Complete media plus dilution series of compounds can be added to wells and incubated, for example at 37 °C in a 5% CO₂ incubator for a sufficient time, for example 10-14 days, preferably with repeated feedings of fresh media containing compound, typically at 3-4 day intervals. Colony formation and total cell mass can be monitored, average colony size and number of colonies can be quantitated according to methods known in the art, for example using image

I03224 do.doc

111

capture technology and image analysis software. Image capture technology and image analysis software, such as Image Pro Plus or media Cybernetics.

5 As discussed herein, these signaling pathways are relevant for various disorders. Accordingly, by interacting with one or more of said signaling pathways, benzimidazolyl derivatives are useful in the prevention and/or the treatment of disorders that are dependent from said signaling pathways.

10 The compounds according to the invention are preferably kinase modulators and more preferably kinase inhibitors. According to the invention, kinases include, but are not limited to one or more Raf-kinases, one or more Tie-kinases, one or more VEGFR-kinases, one or more PDGFR-kinases, p38-kinase and/or SAPK2alpha.

15 Raf-kinases in this respect are respect preferably include or consist of A-Raf, B-Raf and c-Raf1.

Tie-kinases in this respect preferably include or consist of Tie-2 kinase.

20 VEGFR-kinases in this respect preferably include or consist of VEGFR-2 kinase.

25 Due to the kinase modulating or inhibiting properties of the compounds according to the invention, the compounds according to the invention preferably interact with one or more signalling pathways which are preferably cell signalling pathways, preferably by downregulating or inhibiting said signaling pathways. Examples for such signalling pathways include, but are not limited to the raf-kinase pathway, the Tie-kinase pathway, the VEGFR-kinase pathway, the PDGFR-kinase pathway, the p38-kinase pathway, the
30 SAPK2alpha pathway and/or the Ras-pathway.

103224 do.doc

112

Modulation of the raf-kinase pathway plays an important role in various cancerous and noncancerous disorders, preferably cancerous disorders, such as dermatological tumors, haematological tumors, sarcomas, squamous cell cancer, gastric cancer, head cancer, neck cancer, oesophageal cancer, lymphoma, ovary cancer, uterine cancer and/or prostate cancer. Modulation of the raf-kinase pathway plays a even more important role in various cancer types which show a constitutive activation of the raf-kinase dependent signalling pathway, such as melanoma, colorectal cancer, lung cancer, brain cancer, pancreatic cancer, breast cancer, gynaecological cancer, ovarian cancer, thyroid cancer, chronic leukaemia and acute leukaemia, bladder cancer, hepatic cancer and/or renal cancer. Modulation of the raf-kinase pathway plays also an important role in infection diseases, preferably the infection diseases as mentioned above/below and especially in Helicobacter pylori infections, such as Helicobacter pylori infection during peptic ulcer disease.

One or more of the signalling pathways mentioned above/below and especially the VEGFR-kinase pathway plays an important role in angiogenesis. Accordingly, due to the kinase modulating or inhibiting properties of the compounds according to the invention, the compounds according to the invention are suitable for the prophylaxis and/or treatment of pathological processes or disorders caused, mediated and/or propagated by angiogenesis, for example by inducing anti-angiogenesis. Pathological processes or disorders caused, mediated and/or propagated by angiogenesis include, but are not limited to tumors, especially solid tumors, arthritis, especially heumatic or rheumatoid arthritis, diabetic retinopathy, psoriasis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases, and especially solid tumors, rheumatic arthritis, diabetic retinopathy and psoriasis.

103224 do.doc

113

Modulation of the p38-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis, and especially

5 noncancerous disorders such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease.

Modulation of the PDGF-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease, and especially noncancerous disorders such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal

10 disease and/or angiogenesis.

15

Subject of the present invention are therefore benzimidazolyl derivatives according to the invention as promoters or inhibitors, preferably as inhibitors, of the signaling pathways described herein. Preferred subject of the invention

20 are therefore benzimidazolyl derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase pathway. More preferred subject of the invention are therefore benzimidazolyl derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase. Even more preferred subject of the invention

25 are benzimidazolyl derivatives according to invention as promoters or inhibitors, preferably as inhibitors of one or more raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Especially preferred subject of the invention are benzimidazolyl derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of c-raf1.

30

Thus, subject of the present invention are benzimidazolyl derivatives according to the invention as medicaments. Subject of the present invention

103224 do.doc

114

are benzimidazolyl derivatives according to the invention as medicament active ingredients. Further subject of the present invention is the use of one or more benzimidazolyl derivatives according to the invention as a pharmaceutical. Further subject of the present invention is the use of one or more benzimidazolyl derivatives according to the invention in the treatment and/or the prophylaxis of disorders, preferably the disorders described herein, more preferred disorders that are caused, mediated and/ or propagated by signalling pathways discussed herein, even more preferred disorders that are caused, mediated and/or propagated by raf-kinases and especially disorders that are caused, mediated and/or propagated by raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Usually, the disorders discussed herein are divided into two groups, hyperproliferative and non hyperproliferative disorders. In this context, psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases are to be regarded as noncancerous disorders, of which arthritis, inflammation, immunological diseases, autoimmune diseases and immunodeficiency diseases are usually regarded as non hyperproliferative disorders. In this context, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia are to be regarded as cancerous disorders, all of which are usually regarded as hyperproliferative disorders. Especially cancerous cell growth and especially cancerous cell growth mediated by raf-kinase is a disorder which is a target of the present invention. Subject of the present invention therefore are benzimidazolyl derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis of said disorders and the use of benzimidazolyl derivatives according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising

103224 do.doc

115

administering one or more benzimidazolyl derivatives according to the invention to a patient in need of such an administration. Subject of the present invention therefore are benzimidazolyl derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis said disorders and the use of benzimidazolyl derivatives according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more benzimidazolyl derivatives according to the invention to a patient in need of such an administration.

Accordingly, subject of the present invention are pharmaceutical compositions that contain one or more benzimidazolyl derivatives according to the invention. Subject of the present invention are especially pharmaceutical compositions that contain one or more benzimidazolyl derivatives according to the invention and one or more additional compounds (other than the compounds of the instant invention), preferably selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, subject of the present invention is a process for the manufacture of a pharmaceutical composition, wherein one or more benzimidazolyl derivatives according to the invention and one or more compounds (other than the compounds of the instant invention), preferably selected from the group consisting of carriers, excipients, auxiliaries, adjuvants and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, the use of the compounds according to the invention in the treatment of Hyperproliferative disorders is a subject of the instant invention.

I03224 do.doc

116

Accordingly, the use of the compounds according to the invention for producing a medicament for the treatment of hyperproliferative disorders is a subject of the instant invention.

5 Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated NaHCO₃ solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on
10 silica gel, by preparative HPLC and/or by crystallization.

The present invention relates to benzimidazolyl derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition
15 and a method of treatment, comprising administering said pharmaceutical composition to a patient.

20

25

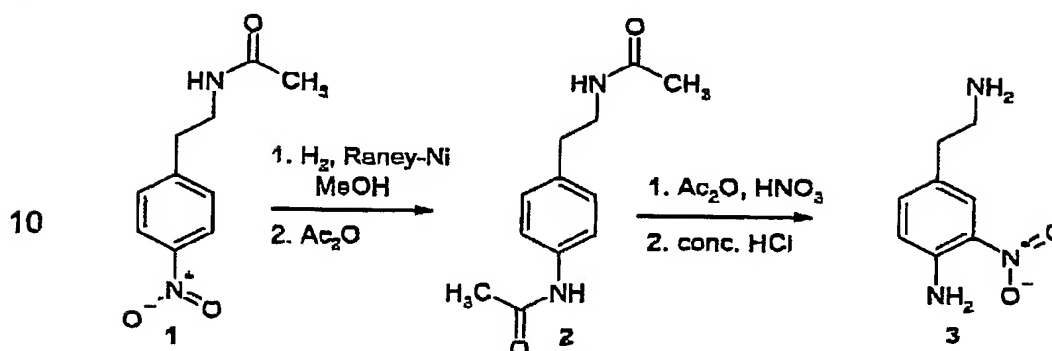
30

103224 do.doc

117

Experimental part**Experimental part****a) Synthesis of the amine unit**

5



15

20 g (96.05 mmol) of 1 were hydrogenated overnight at room temperature using Raney nickel in methanol. The reaction solution was filtered through kieselguhr, the solid was rinsed with MeOH, and the filtrate was subsequently evaporated. The residue crystallised on standing in the refrigerator. The colourless crystals obtained in this way (16.78 g, 98%) were suspended in 50 ml of acetic anhydride and stirred for 30 minutes. The precipitate was filtered off with suction, washed with water and dried under reduced pressure.

20

Yield: 18.6 g (90%) of 2, colourless crystals

25

55 ml of acetic anhydride were initially introduced at 0°C, and 0.9 ml (20.51 mmol) of conc. nitric acid was added dropwise. During this addition, the temperature was held at between 0 and 5°C. The mixture was then re-cooled to 0°C, and 4 g (18.16 mmol) of 2 were added in small portions. The reaction mixture was then stirred at 0°C for 2 hours and subsequently overnight at room temperature. The precipitate was filtered off with suction, rinsed with cold acetic anhydride and water and dried under reduced pressure. Further product was obtained from the filtrate by extraction with dichloromethane.

30

I03224 da.doc

118

Yield: 2.35 g (49%), yellow crystals

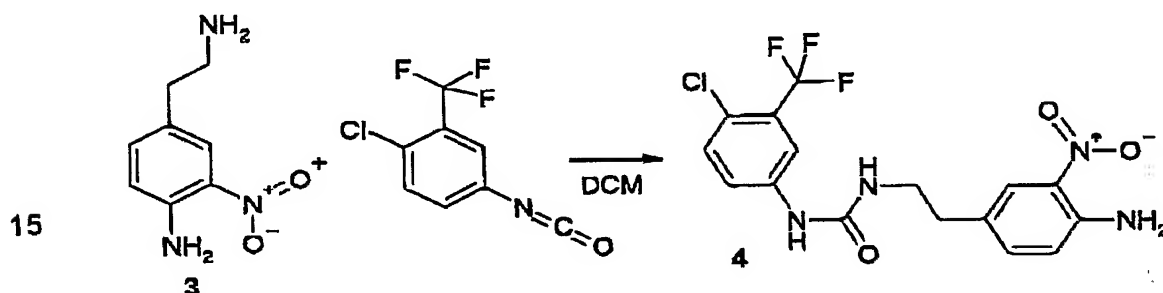
4.5 g (16.96 mmol) of the nitro compound were refluxed overnight in 160 ml of 6N HCl solution. The reaction mixture was adjusted to pH 13 using sodium hydroxide solution and extracted a number of times with dichloromethane.

5 The combined organic phases were dried using Na_2SO_4 , filtered and evaporated.

Yield: 3.1 g (100%) of 3, orange oil.

b) Synthesis of the ureas

10

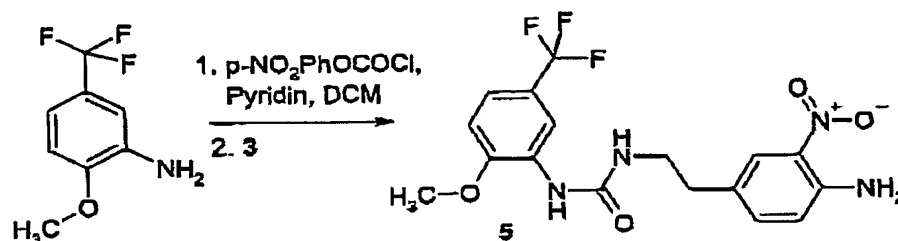


200 mg (1.06 mmol) of 3 were stirred for 2 hours at room temperature together with 235 mg (1.06 mmol) of 4-chloro-3-trifluoromethylphenyl isocyanate in dichloromethane. The reaction mixture was filtered with suction, and the solid was rinsed with dichloromethane.

20

Yield: 0.3 g (67%) of 4, orange solid

25



30

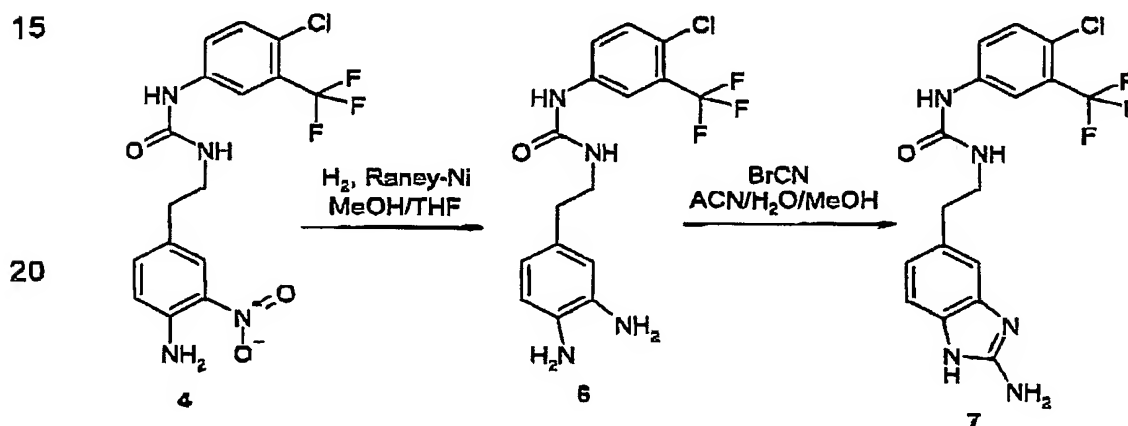
352 mg (1.84 mmol) of 2-methoxy-5-trifluoromethylaniline were dissolved in dichloromethane, 160 mg (2.02 mmol) of pyridine and 408 mg (2.02 mmol) of

I03224 do.doc

119

chloroformic acid, p-nitrophenyl ester, were added successively, and the mixture was stirred at room temperature for 1 hour. When the reaction was complete, 333 mg (1.84 mmol) of 3 and 476 mg (3.68 mmol) of DIPEA were added, and the reaction mixture was stirred at room temperature for 30 minutes. The precipitate obtained was filtered off with suction, rinsed and dried (135 mg). The filtrate was diluted with dichloromethane and washed 3x with water. The organic phase was dried using Na₂SO₄, filtered and evaporated. The residue was digested in a mixture of ethyl acetate, ethanol, dichloromethane and petroleum ether, filtered off with suction, rinsed with dichloromethane and dried under reduced pressure. Yield: 484 mg (66%) of 5, orange solid

c) Benzimidazole syntheses



370 mg (0.92 mmol) of 4 were hydrogenated for 4 hours at room temperature using Raney nickel in methanol/THF 2:1. The reaction solution was filtered through kieselguhr, the solid was rinsed with MeOH, and the filtrate was subsequently evaporated. The residue was purified by column chromatography (10 g of silica gel, eluent: dichloromethane/MeOH 95:5). Yield: 254 mg (74%) of 6, brown oil

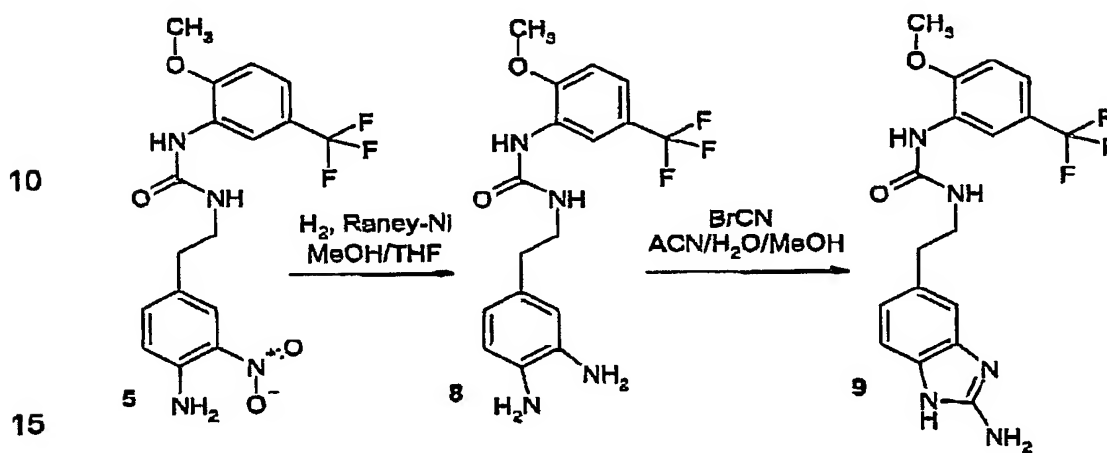
43 mg (0.41 mmol) of cyanogen bromide were dissolved in 0.88 ml of acetonitrile/H₂O 1:10, and 140 mg (0.38 mmol) of 6, dissolved in 0.8 ml of

103224 do.doc

120

methanol, were added over the course of 15 minutes. The reaction mixture was stirred for 2 hours at room temperature, adjusted to pH 8 using saturated NaHCO_3 solution and extracted 2x with ethyl acetate. The combined organic phases were dried using Na_2SO_4 , filtered and evaporated.

5 Yield: 131 mg (88%) of 7, brown crystals



480 mg (1.2 mmol) of 5 were hydrogenated for 8 hours at room temperature using Raney nickel in methanol/THF 4:1. The reaction solution was filtered through kieselguhr, the solid was rinsed with MeOH, and the filtrate was subsequently evaporated.

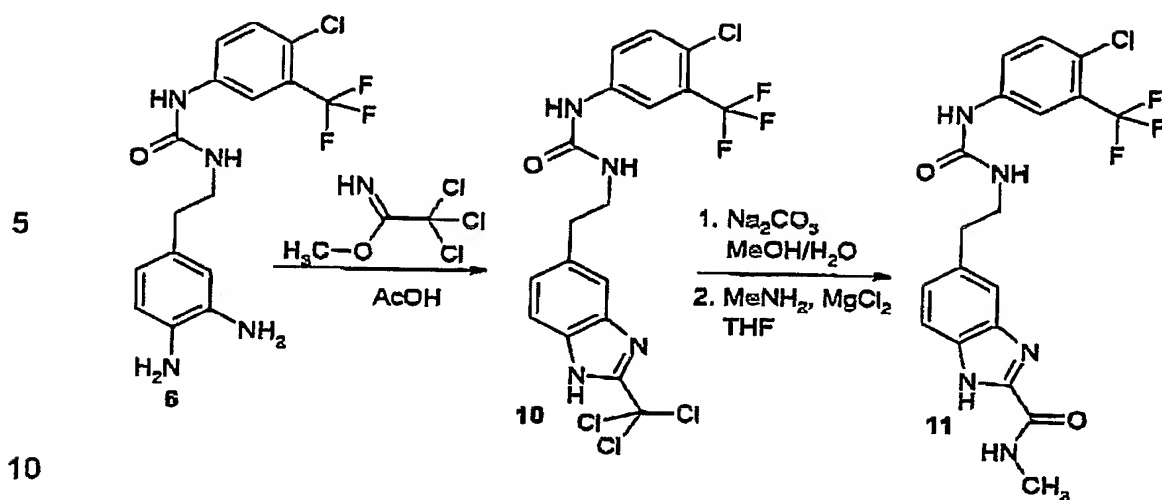
Yield: 435 mg (98%) of 8, brown solid

30 mg (0.28 mmol) of cyanogen bromide were dissolved in 0.6 ml of acetonitrile/ H_2O 1:10, and 100 mg (0.27 mmol) of 8, dissolved in 0.55 ml of methanol, were added over the course of 30 minutes. The reaction mixture was stirred for 3 hours at room temperature, adjusted to pH 8 using saturated NaHCO_3 solution and extracted 2x with ethyl acetate. The combined organic phases were dried using Na_2SO_4 , filtered and evaporated.

Yield: 93 mg (87%) of 9, brown crystals

103224 do.doc

121



100 mg (0.27 mmol) of 6 were dissolved in glacial acetic acid, and 52 mg (0.3 mmol) of methyl 2,2,2-trichloroacetimidate were added over the course of 10 minutes with ice cooling. The reaction mixture was warmed to room temperature, stirred for 30 minutes, poured into ice-water and extracted a number of times with ethyl acetate. The combined organic phases were dried using Na₂SO₄, filtered and evaporated.

The product obtained in this way (138 mg) was dissolved in methanol, 29 mg (0.28 mmol) of sodium carbonate and 0.2 ml of water were added, and the mixture was refluxed for 3.5 hours. The reaction mixture was cooled and diluted with water. The precipitated solid was filtered off with suction, rinsed with a little water and dried overnight at 40°C under reduced pressure.

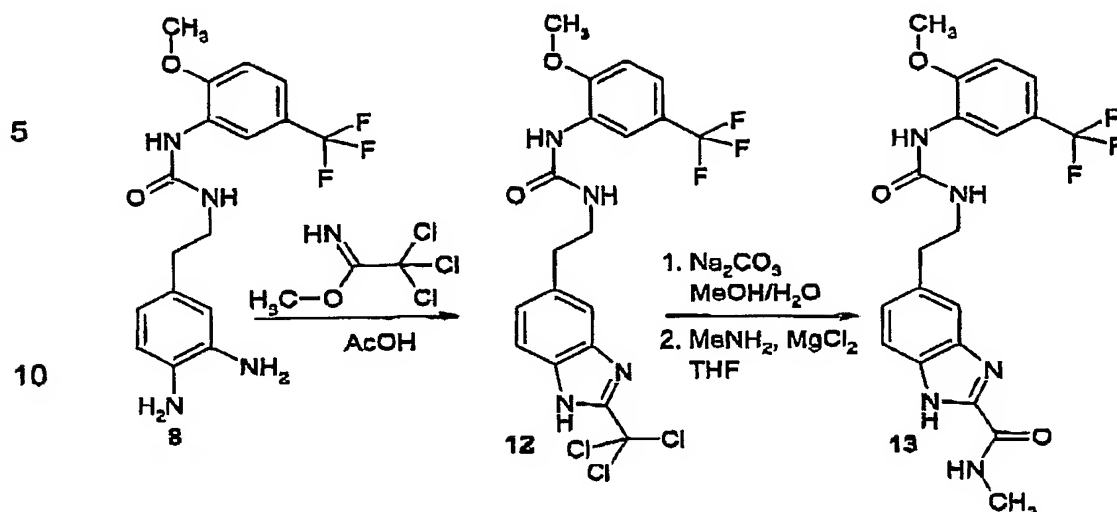
Yield: 103 mg (86%), beige solid

50 mg (0.11 mmol) of the ester were dissolved in THF, and 5.4 mg (0.06 mmol) of anhydrous magnesium chloride were added. After 5 minutes, 0.34 ml (0.34 mmol) of methylamine solution (1M in THF) was added dropwise over the course of 10 minutes, and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice-water and extracted a number of times with ethyl acetate. The combined organic phases were dried using Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography (4 g of silica gel, eluent: ethyl acetate/petroleum ether 8:2, later ethyl acetate).

103224 do.doc

122

Yield: 31 mg (62%) of 11, beige solid



100 mg (0.27 mmol) of 8 were dissolved in glacial acetic acid, and 53 mg (0.3 mmol) of methyl 2,2,2-trichloroacetimidate were added over the course of 10 minutes with ice cooling. The reaction mixture was warmed to room temperature, stirred for 1 hour and poured into ice-water. The precipitate obtained was filtered off with suction, washed with water and dried under reduced pressure.

The product obtained in this way (108 mg) was dissolved in methanol, 23 mg (0.22 mmol) of sodium carbonate and 0.23 ml of water were added, and the mixture was refluxed for 5 hours. The reaction mixture was cooled and diluted with water. The precipitated solid was filtered off with suction, rinsed with a little water and dried overnight at 40°C under reduced pressure.

Yield: 89 mg (75%), beige solid

50 mg (0.11 mmol) of the ester were dissolved in THF, and 5.5 mg (0.06 mmol) of anhydrous magnesium chloride were added. After 5 minutes, 0.34 ml (0.34 mmol) of methylamine solution (1M in THF) was added dropwise over the course of 10 minutes, and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice-

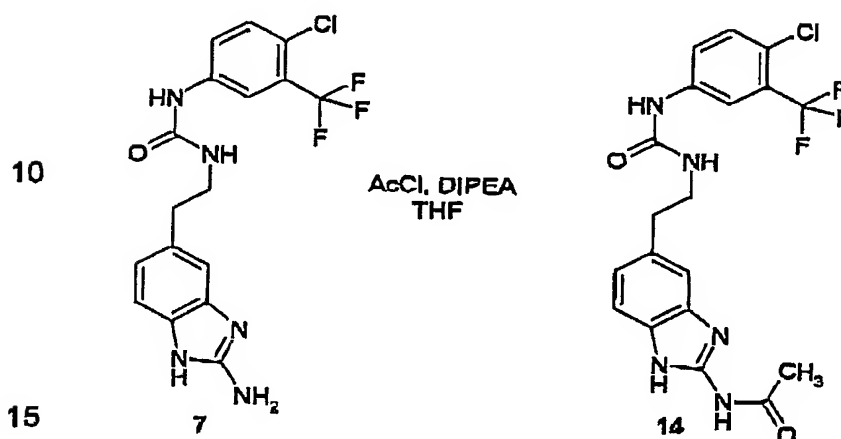
103224 do.doc

123

water, and the precipitate obtained was filtered off with suction, washed with water and dried under reduced pressure.

Yield: 45 mg (90%) of 12, beige solid

5 d) Acylations



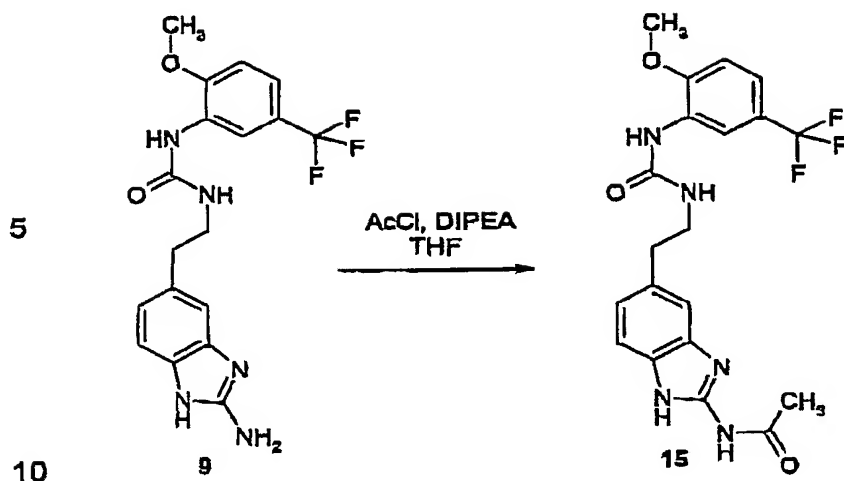
20 60 mg (0.15 mmol) of 7 were dissolved in THF, 19 mg (0.15 mmol) of diisopropylethylamine were added, and 12 mg (0.15 mmol) of acetyl chloride were added dropwise over the course of 5 minutes with ice cooling. The reaction mixture was warmed to room temperature, stirred for 20 minutes, poured into ice-water and extracted a number of times with ethyl acetate. The combined organic phases were dried using Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography (4 g of silica gel, eluent: dichloromethane/methanol 95:5).

25 Yield: 8 mg (12%) of 14, colourless solid

30

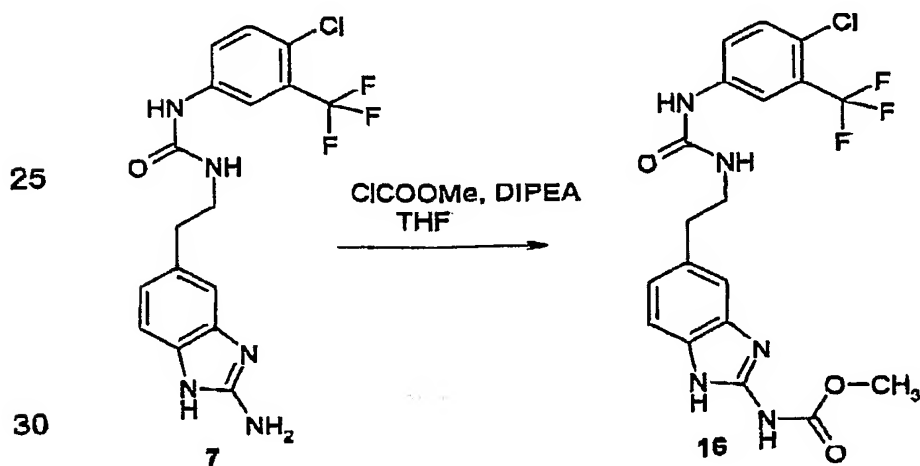
103224 do.doc

124



50 mg (0.13 mmol) of **9** were dissolved in THF, 16 mg (0.13 mmol) of diisopropylethylamine were added, and 10 mg (0.13 mmol) of acetyl chloride were added dropwise over the course of 5 minutes with ice cooling. The reaction mixture was warmed to room temperature, stirred for 20 minutes, poured into ice-water and extracted a number of times with ethyl acetate. The combined organic phases were dried using Na_2SO_4 , filtered and evaporated. The residue was purified by column chromatography (4 g of silica gel, eluent: dichloromethane/methanol 95:5 + 0.1% of NH_3).

Yield: 36 mg (65%) of **15**, beige solid

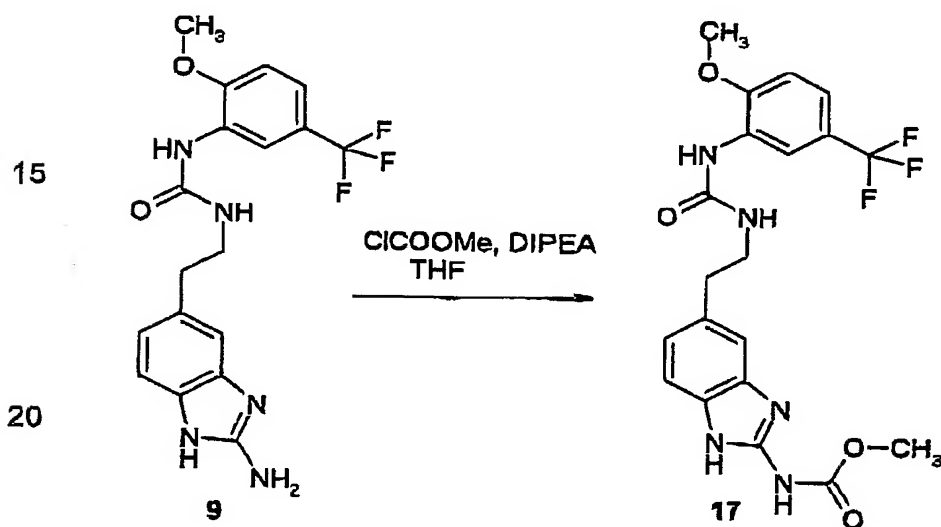


103224 da.doc

125

60 mg (0.15 mmol) of **7** were dissolved in THF, 19 mg (0.15 mmol) of diisopropylethylamine were added, and 14 mg (0.15 mmol) of methyl chloroformate were added dropwise over the course of 5 minutes with ice cooling. The reaction mixture was warmed to room temperature and stirred for 20 minutes. The reaction mixture was poured into ice-water, and the precipitate obtained was filtered off with suction and washed with water. The crude product obtained in this way was purified by column chromatography (4 g of silica gel, eluent: dichloromethane, later dichloromethane/methanol 95:5).

Yield: 34 mg (49%) of **16**, yellow solid



50 mg (0.13 mmol) of **9** were dissolved in THF, 16 mg (0.13 mmol) of diisopropylethylamine were added, and 12 mg (0.13 mmol) of methyl chloroformate were added dropwise over the course of 5 minutes with ice cooling. The reaction mixture was warmed to room temperature and stirred for 20 minutes. The reaction mixture was poured into ice-water, and the precipitate obtained was filtered off with suction and washed with water. The crude product obtained in this way was purified by column chromatography (4 g of silica gel, eluent: dichloromethane, later dichloromethane/methanol 95:5).

I03224 do.doc

126

Yield: 29 mg (51%) of 17, beige solid

Retention times (Rt) as disclosed herein are, if not indicated otherwise, HPLC retention times, obtained according the following methods:

5

General Method:

Gradient: 5.5 min; flow rate: 2.75 ml/min from 90:10 to 0:100 H₂O/ACN
Water + TFA (0.01% by vol.); acetonitrile + TFA (0.01% by vol.)

Column: Chromolith SpeedROD RP 18e 50-4.6

10

Wavelength: 220 nm.

The compounds disclosed herein can preferably be produced according to the procedures described herein or in an analogous manner thereof.

15 Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each

20

Example B: Suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed

25

Example C: Solution

A solution of 1 g of an active compound of the formula I, 9.38 g of NaH₂PO₄ · 2 H₂O, 28.48 g of Na₂HPO₄ · 12 H₂O and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up

30

to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

103224 da.doc

127

Example D: Ointment

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

5

Example E: Tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

10

Example F: Coated tablets

Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

15

Example G: Capsules

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

20

Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

25

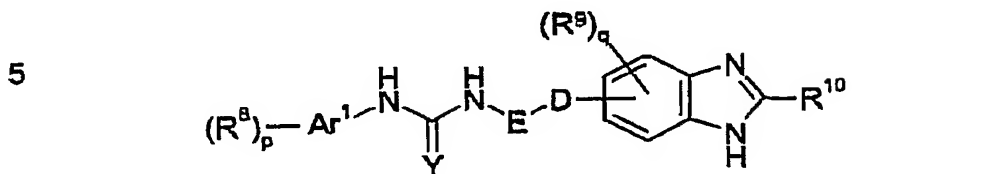
30

103224 do.doc

128

Claims

1. Benzimidazolyl derivatives of formula I



wherein

10

Ar^1 is selected from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

15

E is $(CR^5R^6)_n$, wherein n is 1 or 2,

D is $(CR^5R^6)_k$, wherein k is 0 or 1,

20

R^5, R^6 are in each case independently from one another selected from H and A;

25

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, OHet, $N(R^{11})Het$, $NR^{11}COR^{13}$, $NR^{11}COOR^{13}$, $CONR^{11}R^{12}$, $COOR^{13}$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$, $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,

30

103224 do.doc

129

$(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$,
 $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$,
 $CH=N-OA$, $CH_2CH=N-OA$, $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$,
 $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$,
5 $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$,
 $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$,
 $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$,
 $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2OR^{13}$,
10 $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$,
 $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$,
 $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$,
 $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

15

R^{11} , R^{12} are independently selected from a group consisting of H,
A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

20

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6-
or 7- membered heterocyclus which optionally contains 1 or 2
additional hetero atoms, selected from N, O and S,

25

R^{13} , R^{14} are independently selected from a group consisting of H,
Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

30

A is selected from the group consisting of alkyl, alkenyl, cycloalkyl,
alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl,
preferably from the group consisting of alkyl, alkenyl, cycloalkyl,
alkylenecycloalkyl, alkoxy and alkoxyalkyl,

Ar^3 , Ar^4 are independently from one another aromatic hydrocarbon
residues comprising 5 to 12 and preferably 5 to 10 carbon atoms

I03224 do.doc

130

which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_nA and OOCR¹⁵,

5

Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_nA and OOCR¹⁵,

10

R¹⁵, R¹⁶ are independently selected from a group consisting of H, A, and (CH₂)_mAr⁶, wherein

15

Ar⁶ is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,

20

k, n and m are independently of one another 0, 1, 2, 3, 4, or 5,

Y is selected from O, S, NR²¹, C(R²²)-NO₂, C(R²²)-CN and C(CN)₂, wherein

25

R²¹ is independently selected from the meanings given for R¹³, R¹⁴ and

R²² is independently selected from the meanings given for R¹¹, R¹²,

30

p is independently in each case 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

103224 do.doc

131

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

and

5

Hal is independently selected from a group consisting of F, Cl, Br and I;

10

the tautomeric forms thereof; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

2. Benzimidazolyl derivatives according to claim 1,

wherein

15

Ar¹ is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

20

R⁸, R⁹ and R¹⁰ are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, OHet, N(R¹¹)Het, NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³, (CR⁵R⁶)_kHet, O(CR⁵R⁶)_kHet, N(R¹¹)(CR⁵R⁶)_kHet, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³, O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, and/or are independently selected from a group consisting of NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³,

25

30

I03224 do.doc

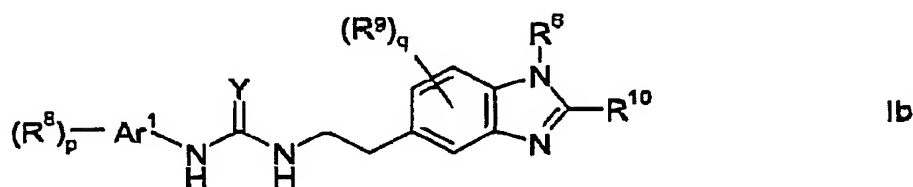
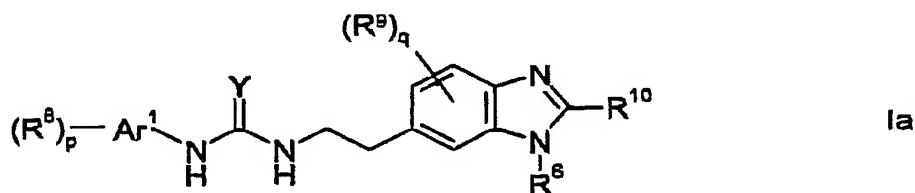
132

$(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$,
 $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$,
 $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$,
5 $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{11}$, $(CH_2)_nN(COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$,
 $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$,
 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,
10 $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,

p is 1, 2, 3 or 4, preferably 1, 2 or 3,

the tautomeric forms thereof; and the pharmaceutically acceptable
 derivatives, solvates, salts and stereoisomers thereof

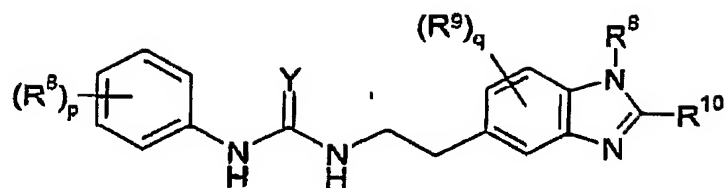
3. Benzimidazolyl derivative according to claim 1 or 2, selected from the compounds of formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, IL, Im, In, Io, Ip, Iq and Ir,



103224 do.doc

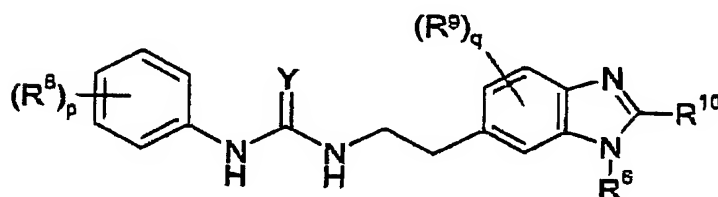
133

5



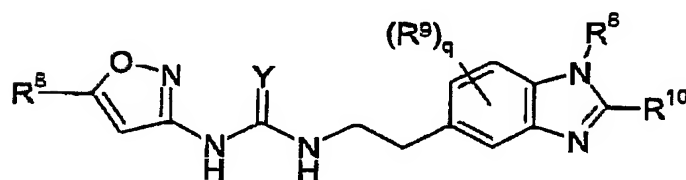
1c

10



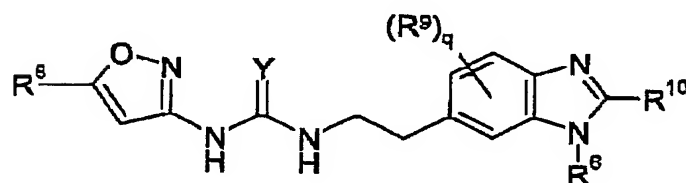
1d

15



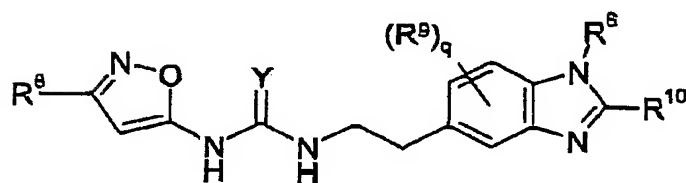
1e

20



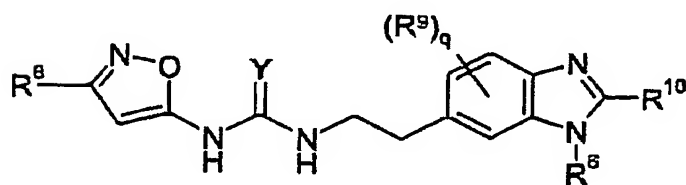
1f

25



1g

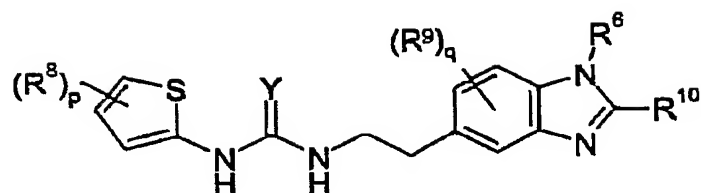
30



1h

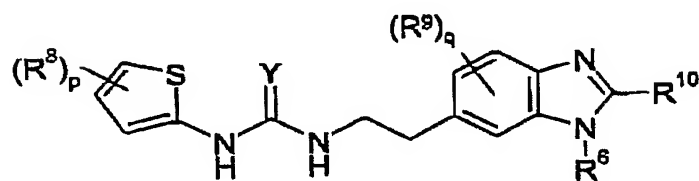
I03224 do.doc

134



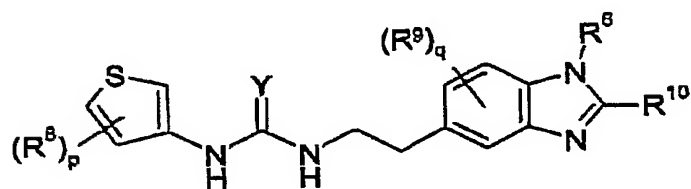
li

5



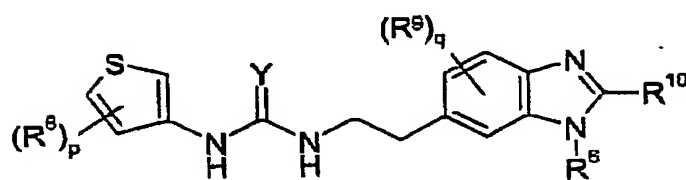
lj

10



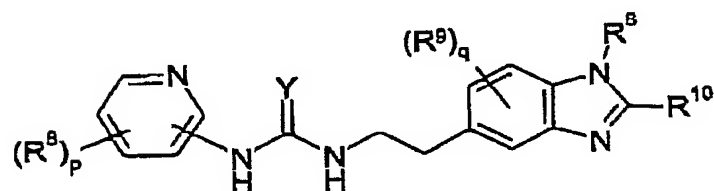
lk

15



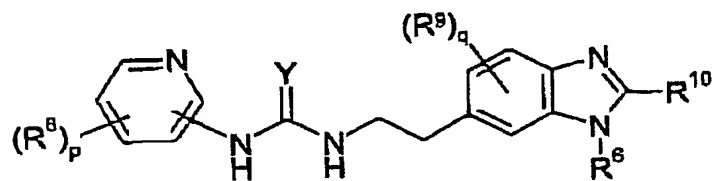
ll

20



lm

25

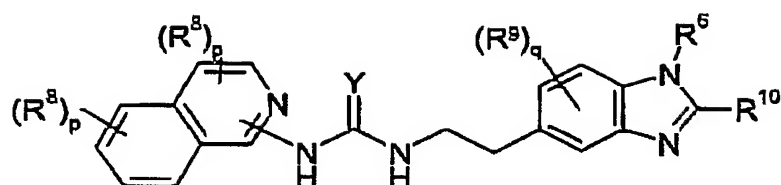


ln

30

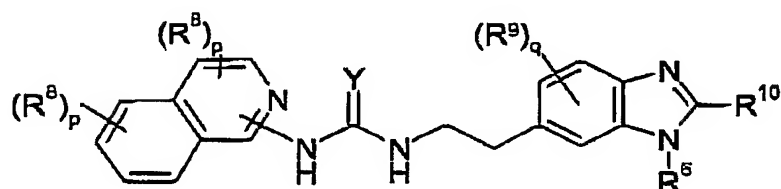
103224 do.doc

135



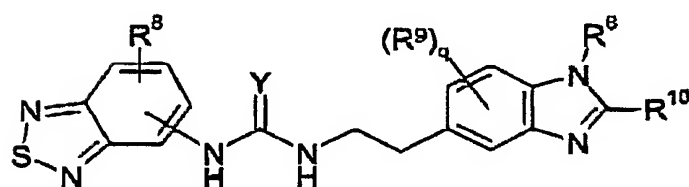
10

5



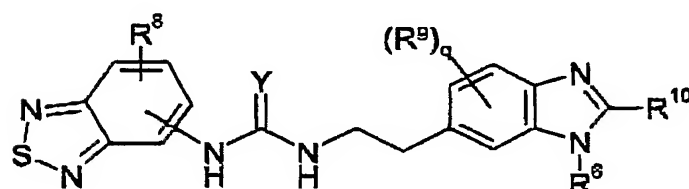
11

10



12

15



13

20

wherein R^8 , R^9 , R^{10} , Y , p and q are as defined in claim 1 or 2, R^{10} is H or as defined in claim 1 or 2; the tautomeric forms thereof; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

25

4. Benzimidazolyl derivative according to claim one of the claims 1 to 3, selected from
 - 6-{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazole-2-carboxylic acid methylester,
 - 6-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazole-2-carboxylic acid methylester,

30

103224 do.doc

136

- 5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazole-2-carboxylic acid methylamide,
(5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazol-2-yl)-carbamic acid methyl ester,
5 N-(5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazol-2-yl)-acetamide,
5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazole-2-carboxylic acid methylamide,
(5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazol-2-yl)-carbamic acid methyl ester,
10 N-(5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzimidazol-2-yl)-acetamide;
the tautomeric forms thereof; and the pharmaceutically acceptable derivatives, salts and solvates thereof.
- 15
5. Benzimidazolyl derivative according to one of the claims 1 to 4 as a medicament.
6. Benzimidazolyl derivative according to one of the claims 1 to 4 as a
20 kinase inhibitor.
7. Benzimidazolyl derivative according to claim 6, characterized in that the kinases are selected from raf-kinases.
- 25 8. Pharmaceutical composition characterised in that it contains one or more compounds according to one of the claims 1 to 4.
9. Pharmaceutical composition according to claim 8, characterised in that it contains one or more additional compounds, selected from the group
30 consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 4.

103224 do.doc

137

10. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 4 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 4, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
11. Use of a compound according to one of the claims 1 to 4 as a pharmaceutical.
12. Use of a compound according to one of the claims 1 to 4 in the treatment and/or prophylaxis of disorders.
13. Use of a compound according to one of the claims 1 to 4 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
14. Use according to claim 12 or 13, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.
15. Use according to claim 12, 13 or 14, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
16. Use according to claim 12, 13, 14 or 15, characterised in that the disorder is cancer.
17. Use according to claim 12, 13, 14 or 15, characterised in that the disorder is noncancerous.

103224 do.doc

138

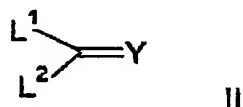
18. Use according to claim 12, 13, 14, 15 or 17, characterised in that the disorders are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, *Helicobacter pylori* infection, Influenza A, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
19. Use according to one of the claims 12 to 18, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, ovarian cancer, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
20. Use according to one of the claims 12 to 17, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors, rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.
21. Use according to one of the claims 12 to 15, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.

103224 do.doc

139

22. Use of a compound according to one of the claims 1 to 4 as a raf-kinase inhibitor.
23. Use according to claim 22, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and c-Raf1.
24. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 4 is administered to a patient in need of such a treatment.
25. Method according to claim 24, characterised in that the one or more compounds according to one of the claims claim 1 to 4 are administered as a pharmaceutical composition according to claim 8 or 9.
26. Method for the treatment and/or prophylaxis of disorders according to claim 25, characterised in that the disorders are as defined in one of the claims 14 to 21.
27. Method for the treatment according to claim 26, characterised in that the disorder is cancerous cell growth mediated by raf-kinase.
28. Method for producing compounds of formula I, characterised in that
a) a compound of formula II,

25



wherein

- L¹ and L² either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

103224 do.doc

140

is reacted with

b) a compound of formula III

5



wherein

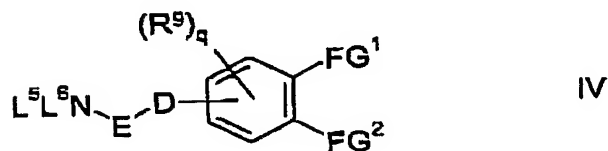
10

L^3 and L^4 are independently from one another H or a metal ion,
and wherein R^B and p are as defined in claim 1,

and

15

c) a compound of formula IV,



20

wherein

L^5 and L^6 are independently from one another H or a metal ion,
 FG^1 is NHR^6 ,

25

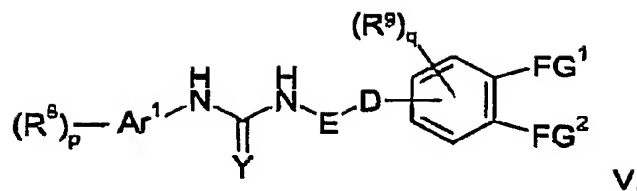
FG^2 is NH_2 oder NO_2 ,

and E , D , R^9 , and q are as defined in claim 1, to obtain a
compound of formula V

30

I03224 do.doc

141



- 10
- d) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 , to transfer the NO_2 group into a NH_2 group, and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2 is NH_2 , with $Hal_3C-C(=NH)OA$ to obtain a compound of formula I, wherein R^{10} is $CHal_3$; or with $HalCN$ to obtain a compound of formula I, wherein R^{10} is NH_2 ;
- 15
- e) and optionally transferring the compound obtained from step d) into a compound of formula I, wherein R^{10} is other than $CHal_3$ or NH_2 ;
- f) and optionally isolating and/or treating the compound of formula I as obtained by said reaction, with an acid, to obtain the salt thereof.
- 20

29. Method for producing compounds of formula I, characterised in that

- a) a compound of formula IIIb

25



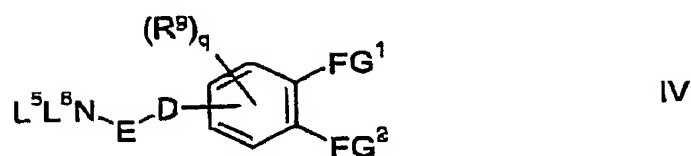
wherein R^8 , Ar^1 , p and Y are as defined in claim 1, is reacted with

30

- b) a compound of formula IV,

103224 do.doc

142



5

wherein

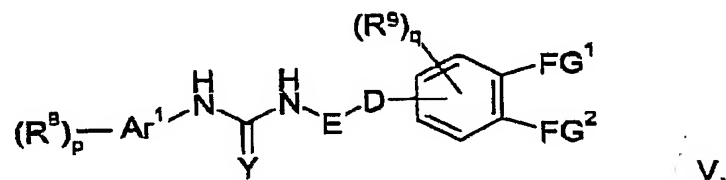
L^5 and L^6 are independently from one another H or a metal ion,

FG^1 is NHR^8 ,

FG^2 is NH_2 oder NO_2 ,

10

and E, D, R^9 , and q are as defined in claim 1, to obtain a compound of formula V



15

- c) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 , to transfer the NO_2 group into a NH_2 group, and reacting the compound of formula V, wherein FG^1 is NHR^8 and FG^2 is NH_2 , with $Hal_3C-C(=NH)OA$ to obtain a compound of formula I, wherein R^{10} is $CHal_3$; or with $HalCN$ to obtain a compound of formula I, wherein R^{10} is NH_2 ;
- d) and optionally transferring the compound obtained from step c) into a compound of formula I, wherein R^{10} is other than $CHal_3$ or NH_2 ,
- e) and optionally isolating and/or treating the compound of formula I as obtained by said reaction, with an acid, to obtain the salt thereof.

25

30

30. Compound of formula IIIb,

103224 do.doc

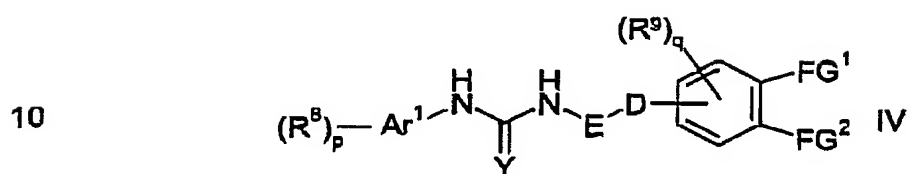
143



wherein R^8 , p , Ar^1 and Y are as defined in claim 1.

5

31. Compound of formula IV,



10

wherein

FG^1 is NHR^8 ,

15

FG^2 is NH_2 oder NO_2 ,

and E , D , R^8 , and q are as defined in claim 1.

20

25

30

I03224 do.doc

144

Abstract

The present invention relates to benzimidazolyl derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

10

15

20

25

30

